Computational Dynamics

--Dynamic Systems, Molecular Dynamics, Computational Sciences, Quantum Dynamics and Complex Systems Dynamics

Dynamics Systems and Molecular Dynamics

Dynamic system

1. REDIRECT Dynamical_system

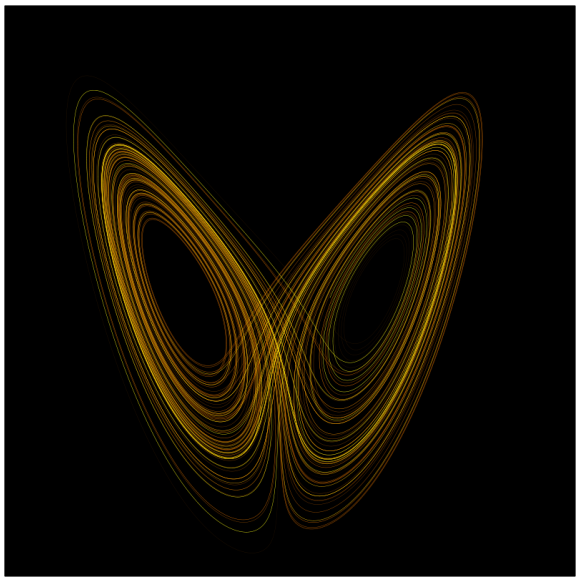
Dynamical systems theory

Dynamical systems theory is an area of applied mathematics used to describe the behavior of complex dynamical systems, usually by employing differential equations or difference equations. When differential equations are employed, the theory is called *continuous dynamical systems*. When difference equations are employed, the theory is called *discrete dynamical systems*. When the time variable runs over a set which is discrete over some intervals and continuous over other intervals or is any arbitrary time-set such as a cantor set then one gets dynamic equations on time scales. Some situations may also be modelled by mixed operators such as differential-difference equations.

This theory deals with the long-term qualitative behavior of dynamical systems, and the studies of the solutions to the equations of motion of systems that are primarily mechanical in nature; although this includes both planetary orbits as well as the behaviour of electronic circuits and the solutions to partial differential equations that arise in biology. Much of modern research is focused on the study of chaotic systems.

This field of study is also called just *Dynamical systems*, *Systems theory* or longer as *Mathematical Dynamical Systems Theory* and the *Mathematical theory of dynamical systems*.

Overview



The Lorenz attractor is an example of a non-linear dynamical system. Studying this system helped give rise to Chaos theory.

Dynamical systems theory and chaos theory deal with the long-term qualitative behavior of dynamical systems. Here, the focus is not on finding precise solutions to the equations defining the dynamical system (which is often hopeless), but rather to answer questions like "Will the system settle down to a steady state in the long term, and if so, what are the possible steady states?", or "Does the long-term behavior of the system depend on its initial condition?"

An important goal is to describe the fixed points, or steady states of a given dynamical system; these are values of the variable which won't change over time. Some of these fixed points are *attractive*, meaning that if the system starts out in a nearby state, it will converge towards the fixed point.

Similarly, one is interested in *periodic points*, states of the system which repeat themselves after several timesteps. Periodic points can also be attractive. Sarkovskii's theorem is an interesting statement about the number of periodic points of a one-dimensional discrete dynamical system.

Even simple nonlinear dynamical systems often exhibit almost random, completely unpredictable behavior that has been called *chaos*. The branch of dynamical systems which deals with the clean definition and investigation of chaos is called chaos theory.

History

The concept of dynamical systems theory has its origins in Newtonian mechanics. There, as in other natural sciences and engineering disciplines, the evolution rule of dynamical systems is given implicitly by a relation that gives the state of the system only a short time into the future.

Before the advent of fast computing machines, solving a dynamical system required sophisticated mathematical techniques and could only be accomplished for a small class of dynamical systems.

Some excellent presentations of mathematical dynamic system theory include Beltrami (1987), Luenberger (1979), Padula and Arbib (1974), and Strogatz (1994).[1]

Concepts

Dynamical systems

The dynamical system concept is a mathematical formalization for any fixed "rule" which describes the time dependence of a point's position in its ambient space. Examples include the → mathematical models that describe the swinging of a clock pendulum, the flow of water in a pipe, and the number of fish each spring in a lake.

A dynamical system has a *state* determined by a collection of real numbers, or more generally by a set of points in an appropriate *state space*. Small changes in the state of the system correspond to small changes in the numbers. The numbers are also the coordinates of a geometrical space—a manifold. The *evolution rule* of the dynamical system is a fixed rule that describes what future states follow from the current state. The rule is deterministic: for a given time interval only one future state follows from the current state.

Dynamicism

Dynamicism, also termed the *dynamic hypothesis* or the *dynamic hypothesis in cognitive science* or *dynamic cognition*, is a new approach in cognitive science exemplified by the work of philosopher Tim van Gelder. It argues that differential equations are more suited to modelling cognition than more traditional computer models.

Nonlinear system

In mathematics, a nonlinear system is a system which is not linear, i.e. a system which does not satisfy the superposition principle. Less technically, a nonlinear system is any problem where the variable(s) to be solved for cannot be written as a linear sum of independent components. A nonhomogenous system, which is linear apart from the presence of a function of the independent variables, is nonlinear according to a strict definition, but such systems are usually studied alongside linear systems, because they can be transformed to a linear system as long as a particular solution is known.

Related fields

Arithmetic dynamics

Arithmetic dynamics is a relatively new field that amalgamates two areas of mathematics, dynamical systems and number theory. Classically, discrete dynamics refers to the study of the iteration of self-maps of the complex plane or real line. Arithmetic dynamics is the study of the number-theoretic properties of integer, rational, p-adic, and/or algebraic points under repeated application of a polynomial or rational function.

Chaos theory

Chaos theory describes the behavior of certain dynamical systems – that is, systems whose state evolves with time – that may exhibit dynamics that are highly sensitive to initial conditions (popularly referred to as the butterfly effect). As a result of this sensitivity, which manifests itself as an exponential growth of perturbations in the initial conditions, the behavior of chaotic systems appears to be random. This happens even though these systems are deterministic, meaning that their future dynamics are

fully defined by their initial conditions, with no random elements involved. This behavior is known as deterministic chaos, or simply *chaos*.

Complex systems

Complex systems is a scientific field, which studies the common properties of systems considered complex in nature, society and science. It is also called *complex systems theory*, *complexity science*, *study of complex systems* and/or *sciences of complexity*. The key problems of such systems are difficulties with their formal modeling and simulation. From such perspective, in different research contexts complex systems are defined on the base of their different attributes.

The study of complex systems is bringing new vitality to many areas of science where a more typical reductionist strategy has fallen short. *Complex systems* is therefore often used as a broad term encompassing a research approach to problems in many diverse disciplines including neurosciences, social sciences, meteorology, chemistry, physics, computer science, psychology, artificial life, evolutionary computation, economics, earthquake prediction, molecular biology and inquiries into the nature of living cells themselves.

Control theory

Control theory is an interdisciplinary branch of engineering and mathematics, that deals with influencing the behavior of dynamical systems.

Ergodic theory

Ergodic theory is a branch of mathematics that studies dynamical systems with an invariant measure and related problems. Its initial development was motivated by problems of → statistical physics.

Functional analysis

Functional analysis is the branch of mathematics, and specifically of analysis, concerned with the study of vector spaces and operators acting upon them. It has its historical roots in the study of functional spaces, in particular transformations of functions, such as the Fourier transform, as well as in the study of differential and integral equations. This usage of the word *functional* goes back to the calculus of variations, implying a function whose argument is a function. Its use in general has been attributed to mathematician and physicist Vito Volterra and its founding is largely attributed to mathematician Stefan Banach.

Graph dynamical systems

The concept of graph dynamical systems (GDS) can be used to capture a wide range of processes taking place on graphs or networks. A major theme in the mathematical and computational analysis of GDS is to relate their structural properties (e.g. the network connectivity) and the global dynamics that result.

Projected dynamical systems

Projected dynamical systems is a mathematical theory investigating the behaviour of dynamical systems where solutions are restricted to a constraint set. The discipline shares connections to and applications with both the static world of optimization and equilibrium problems and the dynamical world of ordinary differential equations. A projected dynamical system is given by the flow to the projected differential equation.

Symbolic dynamics

Symbolic dynamics is the practice of modelling a topological or smooth dynamical system by a discrete space consisting of infinite sequences of abstract symbols, each of which corresponds to a state of the system, with the dynamics (evolution) given by the shift operator.

System dynamics

System dynamics is an approach to understanding the behaviour of complex systems over time. It deals with internal feedback loops and time delays that affect the behaviour of the entire system.[2] What makes using system dynamics different from other approaches to studying complex systems is the use of feedback loops and stocks and flows. These elements help describe how even seemingly simple systems display baffling nonlinearity.

Topological dynamics

→ Topological dynamics is a branch of the theory of dynamical systems in which qualitative, asymptotic properties of dynamical systems are studied from the viewpoint of general topology.

Applications

In biomechanics

In sports biomechanics, dynamical systems theory has emerged in the movement sciences as a viable framework for modeling athletic performance. From a dynamical systems perspective, the human movement system is a highly intricate network of co-dependent sub-systems (e.g. respiratory, circulatory, nervous, skeletomuscular, perceptual) that are composed of a large number of interacting components (e.g. blood cells, oxygen molecules, muscle tissue, metabolic enzymes, connective tissue and bone). In dynamical systems theory, movement patterns emerge through generic processes of self-organization found in physical and biological systems.[3]

In cognitive science

Dynamical system theory has recently emerged in the field of cognitive development. It is the belief that cognitive development is best represented by physical theories rather than theories based on syntax and AI. It also believes that differential equations are the most appropriate tool for modeling human behavior. These equations are interpreted to represent an agent's cognitive trajectory through state space. In other words, dynamicists argue that psychology should be (or is) the description (via differential equations) of the cognitions and behaviors of an agent under certain environmental and internal pressures. The language of chaos theory is also frequently adopted.

In it, the learner's mind reaches a state of disequilibrium where old patterns have broken down. This is the phase transition of cognitive development. Self organization (the spontaneous creation of coherent forms) sets in as activity levels link to each other. Newly formed macroscopic and microscopic structures support each other, speeding up the process. These links form the structure of a new state of order in the mind through a process called *scalloping* (the repeated building up and collapsing of complex performance.) This new, novel state is progressive, discrete, idiosyncratic and unpredictable. [4]

Dynamic systems theory has recently been used to explain a long-unanswered problem in child development referred to as the A-not-B error.[5]

See also

Related subjects

- List of dynamical system topics
- Baker's map
- Dynamical system (definition)
- Embodied Embedded Cognition
- Gingerbreadman map
- Halo orbit
- List of types of systems theory
- Oscillation
- Postcognitivism
- Recurrent neural network
- Combinatorics and dynamical systems

Related scientists

- People in systems and control
- Dmitri Anosov
- Vladimir Arnold
- Nikolay Bogolyubov
- Andrey Kolmogorov
- Nikolay Krylov
- Jürgen Moser
- Yakov G. Sinai
- Stephen Smale
- Hillel Furstenberg

Notes

[1] Jerome R. Busemeyer (2008), "Dynamic Systems" (http://www.cogs.indiana.edu/Publications/techreps2000/241/241.html). To Appear in: *Encyclopedia of cognitive science*, Macmillan. Retrieved 8 May 2008.
[2] MIT System Dynamics in Education Project (SDEP) (http://sysdyn.clexchange.org)
[3] Paul S Glaziera, Keith Davidsb, Roger M Bartlettc (2003). "DYNAMICAL SYSTEMS THEORY: a Relevant Framework for Performance-Oriented Sports Biomechanics Research" (http://www.sportsci.org/jour/03/psg.htm). in: Sportscience 7. Accessdate=2008-05-08.
[4] Lewis, Mark D. (2000-02-25). " The Promise of Dynamic Systems Approaches for an Integrated Account of Human Development (http://home.oise.utoronto.ca/~mlewis/Manuscripts/Promise.pdf)" (PDF). *Child Development* **71** (1): 36–43. doi: 10.1111/1467-8624.00116 (http://dx.doi.org/10.1111/1467-8624.00116). . Retrieved on 2008-04-04.
[5] Smith, Linda B.; Esther Thelen (2003-07-30). " Development as a dynamic system (http://www.indiana.edu/~cogdev/labwork/dynamicsystem.pdf)" (PDF). *TRENDS in Cognitive Sciences* **7** (8): 343–8. doi: 10.1016/S1364-6613(03)00156-6 (http://dx.doi.org/10.1016/S1364-6613(03)00156-6). . Retrieved on 2008-04-04.

Further reading

- Frederick David Abraham (1990), *A Visual Introduction to Dynamical Systems Theory for Psychology*, 1990.
- Beltrami, E. J. (1987). *Mathematics for dynamic modeling*. NY: Academic Press
- Otomar Hájek (1968}, *Dynamical Systems in the Plane*.
- Luenberger, D. G. (1979). *Introduction to dynamic systems*. NY: Wiley.
- Anthony N. Michel, Kaining Wang & Bo Hu (2001), *Qualitative Theory of Dynamical Systems: The Role of Stability Preserving Mappings*.
- Padulo, L. & Arbib, M A. (1974). *System Theory*. Philadelphia: Saunders
- Strogatz, S. H. (1994), *Nonlinear dynamics and chaos*. Reading, MA: Addison Wesley

External links

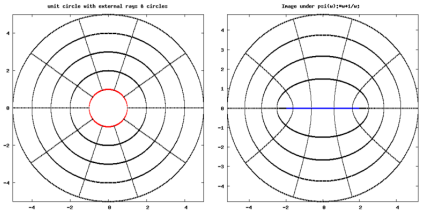
- Dynamic Systems (http://www.cogs.indiana.edu/Publications/techreps2000/241/241.html) Encyclopedia of Cognitive Science entry.
- Definition of dynamical system (http://mathworld.wolfram.com/DynamicalSystem.html) in MathWorld.
- DSWeb (http://www.dynamicalsystems.org/) Dynamical Systems Magazine

List of dynamical systems and differential equation topics

1. REDIRECT List of dynamical systems and differential equations topics

Carathéodory's theorem (conformal mapping)

See also Carathéodory's theorem for other meanings.



simply connected Julia set as an image of unit circle under Riemann map

In mathematics, **Carathéodory's theorem** in complex analysis states that if U is a simply connected open subset of the complex plane **C**, whose boundary is a Jordan curve Γ then the Riemann map

f: $U \to D$

from U to the unit disk D extends continuously to the boundary, giving a homeomorphism

$F : \Gamma \to S^1$

from Γ to the unit circle S^1.

Such a region is called a *Jordan domain*. Equivalently, this theorem states that for such sets U there is a homeomorphism

$F : \mathrm{cl}(U) \to \mathrm{cl}(D)$

from the closure of U to the closed unit disk *cl(D)* whose restriction to the interior is a Riemann map, i.e. it is a bijective holomorphic conformal map.

Another standard formulation of Carathéodory's theorem states that for any pair of simply connected open sets U and V bounded by Jordan curves Γ_1 and Γ_2, a conformal map

$f : U \to V$

extends to a homeomorphism

F: $\Gamma_1 \to \Gamma_2$.

This version can be derived from the one stated above by composing the inverse of one Riemann map with the other.

A more general version of Carathéodory's theorem is the following. Let

$g : D \to U$

be the inverse of the Riemann map, where $D \subset \mathbb{C}$ is the unit disk, and $U \subset \mathbb{C}$ is a simply connected domain. Then g extends continuously to

$G : \mathrm{cl}(D) \to \mathrm{cl}(U)$

if and only if the boundary of U is locally connected.

Context

Intuitively, Carathéodory's theorem says that compared to general simply connected open sets in the complex plane **C**, those bounded by Jordan curves are particularly well-behaved.

Carathéodory's theorem is a basic result in the study of *boundary behavior of conformal maps*, a classical part of complex analysis. In general it is very difficult to decide whether or not the Riemann map from an open set U to the unit disk D extends continuously to the boundary, and how and why it may fail to do so at certain points.

While having a Jordan curve boundary is *sufficient* for such an extension to exist, it is by no means *necessary*. For example, the map

$$f(z) = z^2$$

from the upper half-plane **H** to the open set G that is the complement of the positive real axis is holomorphic and conformal, and it extends to a continuous map from the real line **R** to the positive real axis $\mathbf{R}^+$; however, the set G is not bounded by a Jordan curve.

Dynamics of Markovian particles

Dynamics of Markovian particles (or DMP) is the basis of a theory for kinetics of particles in open heterogeneous systems. It can be looked upon as an application of the notion of stochastic process conceived as a physical entity; e.g. the particle moves because there is a transition probability acting on it.

Two particular features of DMP might be noticed: (1) an ergodic like relation between the motion of particle and the corresponding steady state, and (2) the classic notion of geometric volume appears nowhere (e.g. a concept such as flow of "substance" is not expressed as liters per time unit but as number of particles per time unit). Though being primitive DMP has been applied for solving a classic paradox of the absorption of mercury by fish and by mollusks. The theory has also been applied for a purely probabilistic derivation of the fundamental physical principle: conservation of mass; this might be looked upon as a contribution to the old and ongoing discussion of the relation between physics and probability theory.

Sources

- Bergner---DMP, a kinetics of macroscopic particles in open heterogeneous systems [1]

References

[1] http://www.bergner.se/DMP/download.htm

Statistical physics

Statistical physics is the area of physics that uses methods of probability theory and statistics, and particularly the mathematical tools for dealing with large populations, in solving physical problems. It can describe a wide variety of fields with an inherently stochastic nature. Examples include problems involving nuclear reactions, and topics in the fields of biology, chemistry, neurology and even some social sciences such as sociology.

Historically, one of the first topics in physics where statistical methods were applied was the field of mechanics, which is concerned with the motion of particles or objects when subjected to a force. → **Statistical mechanics** provides a framework for relating the microscopic properties of individual atoms and molecules to the macroscopic or bulk properties of materials that can be observed in everyday life, therefore explaining thermodynamics as a natural result of statistics and mechanics (classical and quantum) at the microscopic level. Because of this history, the term "statistical physics" is therefore sometimes used as a synonym for statistical mechanics or statistical thermodynamics, rather than in the wider sense considered in this article.

A statistical approach can work well in classical systems when the number of degrees of freedom (and so the number of variables) is so large that exact solution is not possible, or not really useful. Statistical mechanics can also describe work in non-linear dynamics, chaos theory, thermal physics, fluid dynamics (particularly at high Knudsen numbers), or plasma physics.

Although some problems in statistical physics can be solved analytically using approximations and expansions, most current research utilizes the large processing power of modern computers to simulate or approximate solutions. A common approach to statistical problems is to use a Monte Carlo simulation to yield insight into the dynamics of a complex system.

See also

- Statistical ensemble
- Statistical field theory
- Mean sojourn time
- → Dynamics of Markovian particles
- Complex network
- Mathematical physics
- Combinatorics and physics

Statistical mechanics

Statistical mechanics (or **statistical thermodynamics**[1]) is the application of probability theory, which includes mathematical tools for dealing with large populations, to the field of mechanics, which is concerned with the motion of particles or objects when subjected to a force. It provides a framework for relating the microscopic properties of individual atoms and molecules to the macroscopic or bulk properties of materials that can be observed in everyday life, therefore explaining thermodynamics as a natural result of statistics and mechanics (classical and quantum) at the microscopic level.

It provides a molecular-level interpretation of thermodynamic quantities such as work, heat, free energy, and entropy, allowing the thermodynamic properties of bulk materials to be related to the spectroscopic data of individual molecules. This ability to make macroscopic predictions based on microscopic properties is the main advantage of statistical mechanics over classical thermodynamics. Both theories are governed by the second law of thermodynamics through the medium of entropy. However, entropy in thermodynamics can only be known empirically, whereas in statistical mechanics, it is a function of the distribution of the system on its micro-states.

Statistical thermodynamics was born in 1870 with the work of Austrian physicist Ludwig Boltzmann, much of which was collectively published in Boltzmann's 1896 *Lectures on Gas Theory*.[2] Boltzmann's original papers on the statistical interpretation of thermodynamics, the H-theorem, transport theory, thermal equilibrium, the equation of state of gases, and similar subjects, occupy about 2,000 pages in the proceedings of the Vienna Academy and other societies. The term "statistical thermodynamics" was proposed for use by the American thermodynamicist and physical chemist J. Willard Gibbs in 1902. According to Gibbs, the term "statistical", in the context of mechanics, i.e. statistical mechanics, was first used by the Scottish physicist James Clerk Maxwell in 1871.

Overview

The essential problem in statistical thermodynamics is to determine the distribution of a given amount of energy E over N identical systems.[3] The goal of statistical thermodynamics is to understand and to interpret the measurable macroscopic properties of materials in terms of the properties of their constituent particles and the interactions between them. This is done by connecting thermodynamic functions to quantum-mechanic equations. Two central quantities in statistical thermodynamics are the Boltzmann factor and the partition function.

Fundamentals

Central topics covered in statistical thermodynamics include:

- Microstates and configurations
- Boltzmann distribution law
- Partition function, Configuration integral or configurational partition function
- Thermodynamic equilibrium - thermal, mechanical, and chemical.
- Internal degrees of freedom - rotation, vibration, electronic excitation, etc.
- Heat capacity – Einstein solids, polyatomic gases, etc.
- Nernst heat theorem
- Fluctuations
- Gibbs paradox
- Degeneracy

Lastly, and most importantly, the formal definition of entropy of a thermodynamic system from a statistical perspective is called statistical entropy, and is defined as:

$$S = k_B \ln \Omega$$

where

k_B is Boltzmann's constant 1.38066×10^{-23} J K^{-1} and

Ω is the number of microstates corresponding to the observed thermodynamic macrostate.

A common mistake is taking this formula as a hard general definition of entropy. This equation is valid only if each microstate is equally accessible (each microstate has an equal probability of occurring).

Boltzmann Distribution

If the system is large the Boltzmann distribution could be used (the Boltzmann distribution is an approximate result)

$$n_i \propto e^{-\frac{U_i}{k_B T}}.$$

This can now be used with $\rho_i = \frac{n_i}{N}$:

$$\rho_i = \frac{n_i}{N} = \frac{e^{-\frac{U_i}{k_B T}}}{\sum_{i=1}^{\text{all levels}} e^{-\frac{U_i}{k_B T}}}.$$

History

In 1738, Swiss physicist and mathematician Daniel Bernoulli published *Hydrodynamica* which laid the basis for the kinetic theory of gases. In this work, Bernoulli positioned the argument, still used to this day, that gases consist of great numbers of molecules moving in all directions, that their impact on a surface causes the gas pressure that we feel, and that what we experience as heat is simply the kinetic energy of their motion.

In 1859, after reading a paper on the diffusion of molecules by Rudolf Clausius, Scottish physicist James Clerk Maxwell formulated the Maxwell distribution of molecular velocities, which gave the proportion of molecules having a certain velocity in a specific range. This was the first-ever statistical law in physics.[4] Five years later, in 1864, Ludwig Boltzmann, a young student in Vienna, came across Maxwell’s paper and was so inspired by it that he

spent much of his long and distinguished life developing the subject further.

Hence, the foundations of statistical thermodynamics were laid down in the late 1800s by those such as Maxwell, Ludwig Boltzmann, Max Planck, Rudolf Clausius, and Willard Gibbs who began to apply statistical and quantum atomic theory to ideal gas bodies. Predominantly, however, it was Maxwell and Boltzmann, working independently, who reached similar conclusions as to the statistical nature of gaseous bodies. Yet, one must consider Boltzmann to be the "father" of statistical thermodynamics with his 1875 derivation of the relationship between entropy S and multiplicity Ω, the number of microscopic arrangements (microstates) producing the same macroscopic state (macrostate) for a particular system.[5]

Fundamental postulate

The fundamental postulate in statistical mechanics (also known as the *equal a priori probability postulate*) is the following:

> *Given an isolated system in equilibrium, it is found with equal probability in each of its accessible microstates.*

This postulate is a fundamental assumption in statistical mechanics - it states that a system in equilibrium does not have any preference for any of its available microstates. Given Ω microstates at a particular energy, the probability of finding the system in a particular microstate is $p = 1/\Omega$.

This postulate is necessary because it allows one to conclude that for a system at equilibrium, the thermodynamic state (macrostate) which could result from the largest number of microstates is also the most probable macrostate of the system.

The postulate is justified in part, for classical systems, by Liouville's theorem (Hamiltonian), which shows that if the distribution of system points through accessible phase space is uniform at some time, it remains so at later times.

Similar justification for a discrete system is provided by the mechanism of detailed balance.

This allows for the definition of the *information function* (in the context of information theory):

$$I = -\sum_i \rho_i \ln \rho_i = \langle \ln \rho \rangle.$$

When all the probabilities (rhos) are equal, I is maximal, and we have minimal information about the system. When our information is maximal (i.e., one rho is equal to one and the rest to zero, such that we know what state the system is in), the function is minimal.

This "information function" is the same as the **reduced entropic function** in thermodynamics.

Statistical ensembles

Microcanonical ensemble

In microcanonical ensemble N, V and E are fixed. Since the second law of thermodynamics applies to isolated systems, the first case investigated will correspond to this case. The *Microcanonical ensemble* describes an isolated system.

The entropy of such a system can only increase, so that the maximum of its entropy corresponds to an equilibrium state for the system.

Because an isolated system keeps a constant energy, the total energy of the system does not fluctuate. Thus, the system can access only those of its micro-states that correspond to a given value *E* of the energy. The internal energy of the system is then strictly equal to its energy.

Let us call $\Omega(E)$ the number of micro-states corresponding to this value of the system's energy. The macroscopic state of maximal entropy for the system is the one in which all micro-states are equally likely to occur, with probability $1/\Omega(E)$, during the system's fluctuations.

$$S = -k_B \sum_{i=1}^{\Omega(E)} \left\{ \frac{1}{\Omega(E)} \ln \frac{1}{\Omega(E)} \right\} = k_B \ln \left(\Omega(E)\right)$$

where

S is the system entropy, and

k_B is Boltzmann's constant.

Canonical ensemble

In canonical ensemble N, V and T are fixed. Invoking the concept of the canonical ensemble, it is possible to derive the probability P_i that a macroscopic system in thermal equilibrium with its environment, will be in a given microstate with energy E_i according to the Boltzmann distribution:

$$P_i = \frac{e^{-\beta E_i}}{\sum_j^{j_{\max}} e^{-\beta E_j}}$$

where $\beta = \frac{1}{kT}$,

The temperature T arises from the fact that the system is in thermal equilibrium with its environment. The probabilities of the various microstates must add to one, and the normalization factor in the denominator is the canonical partition function:

$$Z = \sum_j^{j_{max}} e^{-\beta E_j}$$

where E_i is the energy of the i th microstate of the system. The partition function is a measure of the number of states accessible to the system at a given temperature. The article canonical ensemble contains a derivation of Boltzmann's factor and the form of the partition function from first principles.

To sum up, the probability of finding a system at temperature T in a particular state with energy E_i is

$$P_i = \frac{e^{-\beta E_i}}{Z}.$$

Thermodynamic Connection

The partition function can be used to find the expected (average) value of any microscopic property of the system, which can then be related to macroscopic variables. For instance, the expected value of the microscopic energy E is *interpreted* as the microscopic definition of the thermodynamic variable internal energy U, and can be obtained by taking the derivative of the partition function with respect to the temperature. Indeed,

$$\langle E\rangle = \frac{\sum_i E_i e^{-\beta E_i}}{Z} = -\frac{1}{Z}\frac{dZ}{d\beta}$$

implies, together with the interpretation of $\langle E\rangle$ as U, the following microscopic definition of internal energy:

$$U := -\frac{d\ln Z}{d\beta}.$$

The entropy can be calculated by (see Shannon entropy)

$$\frac{S}{k} = -\sum_i p_i \ln p_i = \sum_i \frac{e^{-\beta E_i}}{Z}(\beta E_i + \ln Z) = \ln Z + \beta U$$

which implies that

$$-\frac{\ln(Z)}{\beta} = U - TS = F$$

is the free energy of the system or in other words,

$$Z = e^{-\beta F}$$

Having microscopic expressions for the basic thermodynamic potentials U (internal energy), S (entropy) and F (free energy) is sufficient to derive expressions for other thermodynamic quantities. The basic strategy is as follows. There may be an intensive or extensive quantity that enters explicitly in the expression for the microscopic energy E_i, for instance magnetic field (intensive) or volume (extensive). Then, the conjugate thermodynamic variables are derivatives of the internal energy. The macroscopic magnetization (extensive) is the derivative of U with respect to the (intensive) magnetic field, and the pressure (intensive) is the derivative of U with respect to volume (extensive). The treatment in this section assumes no exchange of matter (i.e. fixed mass and fixed particle numbers). However, the volume of the system is variable which means the density is also variable.

This probability can be used to find the average value, which corresponds to the macroscopic value, of any property, J, that depends on the energetic state of the system by using the formula:

$$\langle J\rangle = \sum_i p_i J_i = \sum_i J_i \frac{e^{-\beta E_i}}{Z}$$

where $\langle J\rangle$ is the average value of property J. This equation can be applied to the internal energy, U:

$$U = \sum_i E_i \frac{e^{-\beta E_i}}{Z}$$

Subsequently, these equations can be combined with known thermodynamic relationships between U and V to arrive at an expression for pressure in terms of only temperature, volume and the partition function. Similar relationships in terms of the partition function can be derived for other thermodynamic properties as shown in the following table; see also

the detailed explanation in configuration integral [6].

Helmholtz free energy:	$F = -\frac{\ln Z}{\beta}$
Internal energy:	$U = -\left(\frac{\partial \ln Z}{\partial \beta}\right)_{N,V}$
Pressure:	$P = -\left(\frac{\partial F}{\partial V}\right)_{N,T} = \frac{1}{\beta}\left(\frac{\partial \ln Z}{\partial V}\right)_{N,T}$
Entropy:	$S = k(\ln Z + \beta U)$
Gibbs free energy:	$G = F + PV = -\frac{\ln Z}{\beta} + \frac{V}{\beta}\left(\frac{\partial \ln Z}{\partial V}\right)_{N,T}$
Enthalpy:	$H = U + PV$
Constant volume heat capacity:	$C_V = \left(\frac{\partial U}{\partial T}\right)_{N,V}$
Constant pressure heat capacity:	$C_P = \left(\frac{\partial H}{\partial T}\right)_{N,P}$
Chemical potential:	$\mu_i = -\frac{1}{\beta}\left(\frac{\partial \ln Z}{\partial N_i}\right)_{T,V,N}$

To clarify, this is not a grand canonical ensemble.

It is often useful to consider the energy of a given molecule to be distributed among a number of modes. For example, translational energy refers to that portion of energy associated with the motion of the center of mass of the molecule. Configurational energy refers to that portion of energy associated with the various attractive and repulsive forces between molecules in a system. The other modes are all considered to be internal to each molecule. They include rotational, vibrational, electronic and nuclear modes. If we assume that each mode is independent (a questionable assumption) the total energy can be expressed as the sum of each of the components:

$$E = E_t + E_c + E_n + E_e + E_r + E_v$$

Where the subscripts t, c, n, e, r, and v correspond to translational, configurational, nuclear, electronic, rotational and vibrational modes, respectively. The relationship in this equation can be substituted into the very first equation to give:

$$Z = \sum_i e^{-\beta(E_{ti}+E_{ci}+E_{ni}+E_{ei}+E_{ri}+E_{vi})}$$
$$= \sum_i e^{-\beta E_{ti}} e^{-\beta E_{ci}} e^{-\beta E_{ni}} e^{-\beta E_{ei}} e^{-\beta E_{ri}} e^{-\beta E_{vi}}$$

If we can assume all these modes are completely uncoupled and uncorrelated, so all these factors are in a probability sense completely independent, then

$$Z = Z_t Z_c Z_n Z_e Z_r Z_v$$

Thus a partition function can be defined for each mode. Simple expressions have been derived relating each of the various modes to various measurable molecular properties, such as the characteristic rotational or vibrational frequencies.

Expressions for the various molecular partition functions are shown in the following table.

Nuclear	$Z_n = 1 \qquad (T < 10^8 K)$

Electronic	$Z_e = W_0 e^{kTD_e + W_1 e^{-\theta_{e1}/T} + \cdots}$
Vibrational	$Z_v = \prod_j \frac{e^{-\theta_{vj}/2T}}{1 - e^{-\theta_{vj}/T}}$
Rotational (linear)	$Z_r = \frac{T}{\sigma}\theta_r$
Rotational (non-linear)	$Z_r = \frac{1}{\sigma}\sqrt{\frac{\pi T^3}{\theta_A \theta_B \theta_C}}$
Translational	$Z_t = \frac{(2\pi mkT)^{3/2}}{h^3}$
Configurational (ideal gas)	$Z_c = V$

These equations can be combined with those in the first table to determine the contribution of a particular energy mode to a thermodynamic property. For example the "rotational pressure" could be determined in this manner. The total pressure could be found by summing the pressure contributions from all of the individual modes, ie:

$$P = P_t + P_c + P_n + P_e + P_r + P_v$$

Grand canonical ensemble

In grand canonical ensemble V, T and chemical potential are fixed. If the system under study is an open system, (matter can be exchanged), *but* particle number is not conserved, we would have to introduce chemical potentials, μ_j, j = 1,...,n and replace the canonical partition function with the grand canonical partition function:

$$\Xi(V,T,\mu) = \sum_i \exp\left(\beta\left[\sum_{j=1}^{n}\mu_j N_{ij} - E_i\right]\right)$$

where N_{ij} is the number of j^{th} species particles in the i^{th} configuration. Sometimes, we also have other variables to add to the partition function, one corresponding to each conserved quantity. Most of them, however, can be safely interpreted as chemical potentials. In most condensed matter systems, things are nonrelativistic and mass is conserved. However, most condensed matter systems of interest also conserve particle number approximately (metastably) and the mass (nonrelativistically) is none other than the sum of the number of each type of particle times its mass. Mass is inversely related to density, which is the conjugate variable to pressure. For the rest of this article, we will ignore this complication and pretend chemical potentials don't matter. See grand canonical ensemble.

Let's rework everything using a grand canonical ensemble this time. The volume is left fixed and does not figure in at all in this treatment. As before, j is the index for those particles of species j and i is the index for microstate i:

$$U = \sum_i E_i \frac{\exp(-\beta(E_i - \sum_j \mu_j N_{ij}))}{\Xi}$$

$$N_j = \sum_i N_{ij} \frac{\exp(-\beta(E_i - \sum_j \mu_j N_{ij}))}{\Xi}$$

Grand potential:	$\Phi_G = -\frac{\ln \Xi}{\beta}$
Internal energy:	$U = -\left(\frac{\partial \ln \Xi}{\partial \beta}\right)_\mu + \sum_i \frac{\mu_i}{\beta}\left(\frac{\partial \ln \Xi}{\partial \mu_i}\right)_\beta$

Particle number:	$N_i = \frac{1}{\beta}\left(\frac{\partial \ln \Xi}{\partial \mu_i}\right)_\beta$
Entropy:	$S = k(\ln \Xi + \beta U - \beta \sum_i \mu_i N_i)$
Helmholtz free energy:	$F = \Phi_G + \sum_i \mu_i N_i = -\frac{\ln \Xi}{\beta} + \sum_i \frac{\mu_i}{\beta}\left(\frac{\partial \ln \Xi}{\partial \mu_i}\right)_\beta$

Equivalence between descriptions at the thermodynamic limit

All of the above descriptions differ in the way they allow the given system to fluctuate between its configurations.

In the micro-canonical ensemble, the system exchanges no energy with the outside world, and is therefore not subject to energy fluctuations; in the canonical ensemble, the system is free to exchange energy with the outside in the form of heat.

In the thermodynamic limit, which is the limit of large systems, fluctuations become negligible, so that all these descriptions converge to the same description. In other words, the macroscopic behavior of a system does not depend on the particular ensemble used for its description.

Given these considerations, the best ensemble to choose for the calculation of the properties of a macroscopic system is that ensemble which allows the result to be derived most easily.

Random walks

The study of long chain polymers has been a source of problems within the realms of statistical mechanics since about the 1950s. One of the reasons however that scientists were interested in their study is that the equations governing the behaviour of a polymer chain were independent of the chain chemistry. What is more, the governing equation turns out to be a random (diffusive) walk in space. Indeed, the Schrödinger equation is itself a diffusion equation in imaginary time, $t' = it$.

Random walks in time

The first example of a random walk is one in space, whereby a particle undergoes a random motion due to external forces in its surrounding medium. A typical example would be a pollen grain in a beaker of water. If one could somehow "dye" the path the pollen grain has taken, the path observed is defined as a random walk.

Consider a toy problem, of a train moving along a 1D track in the x-direction. Suppose that the train moves either a distance of + or - a fixed distance **b**, depending on whether a coin lands heads or tails when flipped. Lets start by considering the statistics of the steps the toy train takes (where S_i is the ith step taken):

$\langle S_i \rangle = 0$; due to *a priori* equal probabilities
$\langle S_i S_j \rangle = b^2 \delta_{ij}$.

The second quantity is known as the correlation function. The delta is the kronecker delta which tells us that if the indices *i* and *j* are different, then the result is 0, but if *i* = *j* then the kronecker delta is 1, so the correlation function returns a value of b^2. This makes sense, because if *i* = *j* then we are considering the same step. Rather trivially then it can be shown

that the average displacement of the train on the x-axis is 0;

$$x = \sum_{i=1}^{N} S_i$$
$$\langle x \rangle = \langle \sum_{i=1}^{N} S_i \rangle$$
$$\langle x \rangle = \sum_{i=1}^{N} \langle S_i \rangle.$$

As stated $\langle S_i \rangle$ is 0, so the sum of 0 is still 0. It can also be shown, using the same method demonstrated above, to calculate the root mean square value of problem. The result of this calculation is given below

$$x_{rms} = \sqrt{\langle x^2 \rangle} = b\sqrt{N}.$$

From the diffusion equation it can be shown that the distance a diffusing particle moves in a media is proportional to the root of the time the system has been diffusing for, where the proportionality constant is the root of the diffusion constant. The above relation, although cosmetically different reveals similar physics, where *N* is simply the number of steps moved (is loosely connected with time) and *b* is the characteristic step length. As a consequence we can consider diffusion as a random walk process.

Random walks in space

Random walks in space can be thought of as snapshots of the path taken by a random walker in time. One such example is the spatial configuration of long chain polymers.

There are two types of random walk in space: *self-avoiding random walks*, where the links of the polymer chain interact and do not overlap in space, and *pure random* walks, where the links of the polymer chain are non-interacting and links are free to lie on top of one another. The former type is most applicable to physical systems, but their solutions are harder to get at from first principles.

By considering a freely jointed, non-interacting polymer chain, the end-to-end vector is $\mathbf{R} = \sum_{i=1}^{N} \mathbf{r}_i$ where $\mathbf{r}_i$ is the vector position of the *i*-th link in the chain. As a result of the central limit theorem, if N >> 1 then we expect a Gaussian distribution for the end-to-end vector. We can also make statements of the statistics of the links themselves;
$\langle \mathbf{r}_i \rangle = 0$; by the isotropy of space
$\langle \mathbf{r}_i \cdot \mathbf{r}_j \rangle = 3b^2 \delta_{ij}$; all the links in the chain are uncorrelated with one another
Using the statistics of the individual links, it is easily shown that $\langle \mathbf{R} \rangle = 0$ and $\langle \mathbf{R} \cdot \mathbf{R} \rangle = 3Nb^2$. Notice this last result is the same as that found for random walks in time.

Assuming, as stated, that that distribution of end-to-end vectors for a very large number of identical polymer chains is gaussian, the probability distribution has the following form

$$P = \frac{1}{\left(\frac{2\pi N b^2}{3}\right)^{3/2}} \exp \frac{-3\mathbf{R} \cdot \mathbf{R}}{2Nb^2}$$

What use is this to us? Recall that according to the principle of equally likely *a priori* probabilities, the number of microstates, Ω, at some physical value is directly proportional to the probability distribution at that physical value, *viz*;

$$\Omega(\mathbf{R}) = cP(\mathbf{R})$$

where c is an arbitrary proportionality constant. Given our distribution function, there is a maxima corresponding to $\mathbf{R} = 0$. Physically this amounts to there being more microstates which have an end-to-end vector of 0 than any other microstate. Now by considering

$S(\mathbf{R}) = k_B \ln \Omega(\mathbf{R})$

$\Delta S(\mathbf{R}) = S(\mathbf{R}) - S(0)$

$\Delta F = -T\Delta S(\mathbf{R})$

where *F* is the Helmholtz free energy it is trivial to show that

$$\Delta F = k_B T \frac{3R^2}{2Nb^2} = \frac{1}{2} K R^2 \quad ; K = \frac{3k_B T}{Nb^2}$$

A Hookian spring!

This result is known as the **Entropic Spring Result** and amounts to saying that upon stretching a polymer chain you are doing work on the system to drag it away from its (preferred) equilibrium state. An example of this is a common elastic band, composed of long chain (rubber) polymers. By stretching the elastic band you are doing work on the system and the band behaves like a conventional spring. What is particularly astonishing about this result however, is that the work done in stretching the polymer chain can be related entirely to the change in entropy of the system as a result of the stretching.

Classical thermodynamics vs.statistical thermodynamics

As an example, from a classical thermodynamics point of view one might ask what is it about a thermodynamic system of gas molecules, such as ammonia NH_3, that determines the free energy characteristic of that compound? Classical thermodynamics does not provide the answer. If, for example, we were given spectroscopic data, of this body of gas molecules, such as bond length, bond angle, bond rotation, and flexibility of the bonds in NH_3 we should see that the free energy could not be other than it is. To prove this true, we need to bridge the gap between the microscopic realm of atoms and molecules and the macroscopic realm of classical thermodynamics. From physics, → statistical mechanics provides such a bridge by teaching us how to conceive of a thermodynamic *system* as an assembly of *units*. More specifically, it demonstrates how the thermodynamic parameters of a system, such as temperature and pressure, are interpretable in terms of the parameters descriptive of such constituent atoms and molecules.[7]

In a bounded system, the crucial characteristic of these microscopic units is that their energies are quantized. That is, where the energies accessible to a macroscopic system form a virtual continuum of possibilities, the energies open to any of its submicroscopic components are limited to a discontinuous set of alternatives associated with integral values of some quantum number.

See also

- Chemical thermodynamics
- Configuration entropy
- Dangerously irrelevant
- Paul Ehrenfest
- Equilibrium thermodynamics
- Fluctuation dissipation theorem
- Important Publications in Statistical Mechanics
- Ising Model
- Mean field theory
- Nanomechanics
- Non-equilibrium thermodynamics
- → Quantum thermodynamics
- → Statistical physics
- Thermochemistry
- Widom insertion method
- → Monte Carlo method
- → Molecular modelling

A Table of Statistical Mechanics Articles

	Maxwell Boltzmann	**Bose-Einstein**	**Fermi-Dirac**
Particle		Boson	Fermion
Statistics	Partition function Statistical properties Microcanonical ensemble | Canonical ensemble | Grand canonical ensemble		
Statistics	Maxwell-Boltzmann statistics Maxwell-Boltzmann distribution Boltzmann distribution Gibbs paradox	Bose-Einstein statistics	Fermi-Dirac statistics
Thomas-Fermi approximation	gas in a box gas in a harmonic trap		
Gas	Ideal gas	Bose gas Debye model Bose-Einstein condensate Planck's law of black body radiation	Fermi gas Fermion condensate
Chemical Equilibrium	Classical Chemical equilibrium		

Notes

[1] The terms "Statistical mechanics" and "statistical thermodynamics" are used interchangeably. "Statistical physics" is a broader term which includes statistical mechanics, but is sometimes also used as a synonym for statistical mechanics

[2] On history of fundamentals of statistical thermodynamics (http://www.worldscibooks.com/phy_etextbook/2012/2012_chap01.pdf) (section 1.2)

[3] Schrodinger, Erwin (1946). *Statistical Thermodynamics*. Dover Publications, Inc.. ISBN 0-486-66101-6. OCLC 20056858 (http://worldcat.org/oclc/20056858).

[4] Mahon, Basil (2003). *The Man Who Changed Everything – the Life of James Clerk Maxwell*. Hoboken, NJ: Wiley. ISBN 0-470-86171-1. OCLC 52358254 62045217 (http://worldcat.org/oclc/52358254+62045217).

[5] Perrot, Pierre (1998). *A to Z of Thermodynamics*. Oxford University Press. ISBN 0-19-856552-6. OCLC 123283342 38073404 (http://worldcat.org/oclc/123283342+38073404).

[6] http://clesm.mae.ufl.edu/wiki.pub/index.php/Configuration_integral_%28statistical_mechanics%29

[7] Nash, Leonard K. (1974). *Elements of Statistical Thermodynamics, 2nd Ed.*. Dover Publications, Inc.. ISBN 0-486-44978-5. OCLC 61513215 (http://worldcat.org/oclc/61513215).

References

- Chandler, David (1987). *Introduction to Modern Statistical Mechanics*. Oxford University Press. ISBN 0-19-504277-8. OCLC 13946448 (http://worldcat.org/oclc/13946448).
- Huang, Kerson (1990). *Statistical Mechanics*. Wiley, John & Sons. ISBN 0-471-81518-7. OCLC 15017884 (http://worldcat.org/oclc/15017884).
- Kittel, Charles; Herbert Kroemer (1980). *Thermal Physics* (2nd ed.). San Francisco: W.H. Freeman. ISBN 0716710889. OCLC 5171399 (http://worldcat.org/oclc/5171399).
- McQuarrie, Donald (2000). *Statistical Mechanics (2nd rev. Ed.)*. University Science Books. ISBN 1-891389-15-7. OCLC 43370175 (http://worldcat.org/oclc/43370175).
- Dill, Ken; Bromberg, Sarina (2003). *Molecular Driving Forces*. Garland Science. ISBN 0-8153-2051-5. OCLC 47915710 (http://worldcat.org/oclc/47915710).
- List of notable textbooks in statistical mechanics

Further reading

- Ben-Naim, Arieh (2007). *Statistical Thermodynamics Based on Information*. ISBN 978-981-270-707-9
- Boltzmann, Ludwig; and Dieter Flamm (2000). *Entropie und Wahrscheinlichkeit*. ISBN 978-3817132867
- Boltzmann, Ludwig (1896, 1898). *[Lectures on gas theory]*. New York: Dover. ISBN 0486684555. OCLC 31434905 (http://worldcat.org/oclc/31434905). translated by Stephen G. Brush (1964) Berkeley: University of California Press; (1995) New York: Dover ISBN 0-486-68455-5
- Gibbs, J. Willard (1981) [1902]. *Elementary principles in statistical dynamics*. Woodbridge, Connecticut: Ox Bow Press. ISBN 0-918024-20-X.
- Landau, Lev Davidovich; and Lifshitz, Evgeny Mikhailovich (1980) [1976]. *Statistical Physics*. **5** (3 ed.). Oxford: Pergamon Press. ISBN 0-7506-3372-7. Translated by J.B. Sykes and M.J. Kearsley
- Reichl, Linda E (1998) [1980]. *A modern course in statistical physics* (2 ed.). Chichester: Wiley. ISBN 0-471-59520-9.

External links

- Philosophy of Statistical Mechanics (http://plato.stanford.edu/entries/statphys-statmech/) article by Lawrence Sklar for the Stanford Encyclopedia of Philosophy.
- Sklogwiki - Thermodynamics, statistical mechanics, and the computer simulation of materials. (http://www.sklogwiki.org/) SklogWiki is particularly orientated towards liquids and soft condensed matter.
- Statistical Thermodynamics (http://history.hyperjeff.net/statmech.html) - Historical Timeline

Molecular dynamics

Molecular dynamics (**MD**) is a form of computer simulation in which atoms and molecules are allowed to interact for a period of time by approximations of known physics, giving a view of the motion of the atoms. Because molecular systems generally consist of a vast number of particles, it is impossible to find the properties of such complex systems analytically. When the number of bodies are more than two no analytical solutions can be found and result in chaotic motion (see n-body problem). MD simulation circumvents this problem by using numerical methods. It represents an interface between laboratory experiments and theory, and can be understood as a "virtual experiment".

Molecular dynamics is that branch of chemistry,which deals with the study of computer simulation in which atoms and molecules are allowed to interact for a period of time by approximations of known physics.

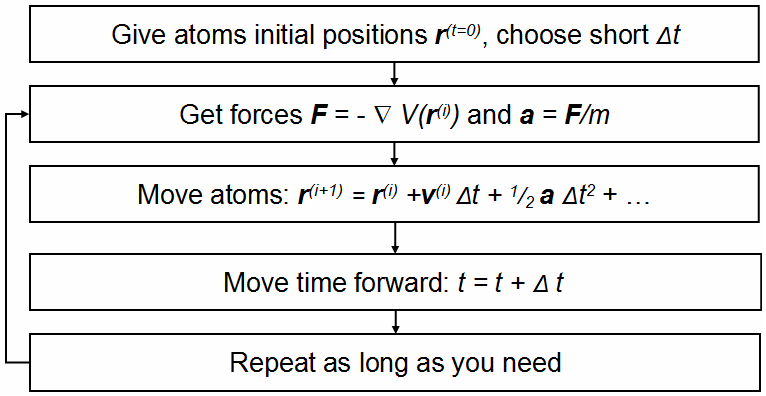
MD probes the relationship between molecular structure, movement and function. Molecular dynamics is a multidisciplinary method. Its laws and theories stem from mathematics, physics, and chemistry, and it employs algorithms from computer science and information theory. It was originally conceived within theoretical physics in the late 1950s[1] and early 1960s [2] , but is applied today mostly in materials science and modeling of biomolecules.

Before it became possible to simulate molecular dynamics with computers, some undertook the hard work of trying it with physical models such as macroscopic spheres. The idea was to arrange them to replicate the properties of a liquid. J.D. Bernal said, in 1962: "... I took a number of rubber balls and stuck them together with rods of a selection of different lengths ranging from 2.75 to 4 inches. I tried to do this in the first place as casually as possible, working in my own office, being interrupted every five minutes or so and not remembering what I had done before the interruption."[3] Fortunately, now computers keep track of bonds during a simulation.

Molecular dynamics is a specialized discipline of molecular modeling and computer simulation based on → statistical mechanics; the main justification of the MD method is that statistical ensemble averages are equal to time averages of the system, known as the ergodic hypothesis. MD has also been termed "statistical mechanics by numbers" and "Laplace's vision of Newtonian mechanics" of predicting the future by animating nature's forces[4] [5] and allowing insight into molecular motion on an atomic scale. However, long MD simulations are mathematically ill-conditioned, generating cumulative errors in numerical integration that can be minimized with proper selection of algorithms and

parameters, but not eliminated entirely. Furthermore, current potential functions are, in many cases, not sufficiently accurate to reproduce the dynamics of molecular systems, so the much more computationally demanding Ab Initio Molecular Dynamics method must be used. Nevertheless, molecular dynamics techniques allow detailed time and space resolution into representative behavior in phase space.

Areas of Application



Highly simplified description of the molecular dynamics simulation algorithm. The simulation proceeds iteratively by alternatively calculating forces and solving the equations of motion based on the accelerations obtained from the new forces. In practise, almost all MD codes use much more complicated versions of the algorithm, including two steps (predictor and corrector) in solving the equations of motion and many additional steps for e.g. temperature and pressure control, analysis and output.

There is a significant difference between the focus and methods used by chemists and physicists, and this is reflected in differences in the jargon used by the different fields. In chemistry and biophysics, the interaction between the particles is either described by a "force field" (**classical MD**), a → quantum chemical model, or a mix between the two. These terms are not used in physics, where the interactions are usually described by the name of the theory or approximation being used and called the potential energy, or just "potential".

Beginning in theoretical physics, the method of MD gained popularity in materials science and since the 1970s also in biochemistry and biophysics. In chemistry, MD serves as an important tool in protein structure determination and refinement using experimental tools such as X-ray crystallography and NMR. It has also been applied with limited success as a method of refining protein structure predictions. In physics, MD is used to examine the dynamics of atomic-level phenomena that cannot be observed directly, such as thin film growth and ion-subplantation. It is also used to examine the physical properties of nanotechnological devices that have not or cannot yet be created.

In applied mathematics and theoretical physics, molecular dynamics is a part of the research realm of dynamical systems, ergodic theory and → statistical mechanics in general. The concepts of energy conservation and molecular entropy come from thermodynamics. Some techniques to calculate conformational entropy such as principal components analysis come from information theory. Mathematical techniques such as the transfer operator become applicable when MD is seen as a Markov chain. Also, there is a large community of mathematicians working on volume preserving, symplectic integrators for more computationally efficient MD simulations.

MD can also be seen as a special case of the discrete element method (DEM) in which the particles have spherical shape (e.g. with the size of their van der Waals radii.) Some authors in the DEM community employ the term MD rather loosely, even when their simulations do not model actual molecules.

Design Constraints

Design of a molecular dynamics simulation should account for the available computational power. Simulation size (n=number of particles), timestep and total time duration must be selected so that the calculation can finish within a reasonable time period. However, the simulations should be long enough to be relevant to the time scales of the natural processes being studied. To make statistically valid conclusions from the simulations, the time span simulated should match the kinetics of the natural process. Otherwise, it is analogous to making conclusions about how a human walks from less than one footstep. Most scientific publications about the dynamics of proteins and DNA use data from simulations spanning nanoseconds (1E-9 s) to microseconds (1E-6 s). To obtain these simulations, several CPU-days to CPU-years are needed. Parallel algorithms allow the load to be distributed among CPUs; an example is the spatial decomposition in LAMMPS.

During a classical MD simulation, the most CPU intensive task is the evaluation of the potential (force field) as a function of the particles' internal coordinates. Within that energy evaluation, the most expensive one is the non-bonded or non-covalent part. In Big O notation, common molecular dynamics simulations scale by $O(n^2)$ if all pair-wise electrostatic and van der Waals interactions must be accounted for explicitly. This computational cost can be reduced by employing electrostatics methods such as Particle Mesh Ewald ($O(n\log(n))$) or good spherical cutoff techniques ($O(n)$).

Another factor that impacts total CPU time required by a simulation is the size of the integration timestep. This is the time length between evaluations of the potential. The timestep must be chosen small enough to avoid discretization errors (i.e. smaller than the fastest vibrational frequency in the system). Typical timesteps for classical MD are in the order of 1 femtosecond (1E-15 s). This value may be extended by using algorithms such as SHAKE, which fix the vibrations of the fastest atoms (e.g. hydrogens) into place. Multiple time scale methods have also been developed, which allow for extended times between updates of slower long-range forces.[6] [7] [8]

For simulating molecules in a solvent, a choice should be made between explicit solvent and implicit solvent. Explicit solvent particles (such as the TIP3P and SPC/E water models) must be calculated expensively by the force field, while implicit solvents use a mean-field approach. Using an explicit solvent is computationally expensive, requiring inclusion of about ten times more particles in the simulation. But the granularity and viscosity of explicit solvent is essential to reproduce certain properties of the solute molecules. This is especially important to reproduce kinetics.

In all kinds of molecular dynamics simulations, the simulation box size must be large enough to avoid boundary condition artifacts. Boundary conditions are often treated by choosing fixed values at the edges, or by employing periodic boundary conditions in which one side of the simulation loops back to the opposite side, mimicking a bulk phase.

Microcanonical ensemble (NVE)

In the **microcanonical**, or **NVE** ensemble, the system is isolated from changes in moles (N), volume (V) and energy (E). It corresponds to an adiabatic process with no heat exchange. A microcanonical molecular dynamics trajectory may be seen as an exchange of potential and kinetic energy, with total energy being conserved. For a system of N particles with coordinates X and velocities V, the following pair of first order differential equations may be written in Newton's notation as

$$F(X) = -\nabla U(X) = M\dot{V}(t)$$
$$V(t) = \dot{X}(t).$$

The potential energy function $U(X)$ of the system is a function of the particle coordinates X. It is referred to simply as the "potential" in Physics, or the "force field" in Chemistry. The first equation comes from Newton's laws; the force F acting on each particle in the system can be calculated as the negative gradient of $U(X)$.

For every timestep, each particle's position X and velocity V may be integrated with a symplectic method such as Verlet. The time evolution of X and V is called a trajectory. Given the initial positions (e.g. from theoretical knowledge) and velocities (e.g. randomized Gaussian), we can calculate all future (or past) positions and velocities.

One frequent source of confusion is the meaning of temperature in MD. Commonly we have experience with macroscopic temperatures, which involve a huge number of particles. But temperature is a statistical quantity. If there is a large enough number of atoms, statistical temperature can be estimated from the *instantaneous temperature*, which is found by equating the kinetic energy of the system to $nk_BT/2$ where n is the number of degrees of freedom of the system.

A temperature-related phenomenon arises due to the small number of atoms that are used in MD simulations. For example, consider simulating the growth of a copper film starting with a substrate containing 500 atoms and a deposition energy of 100 eV. In the real world, the 100 eV from the deposited atom would rapidly be transported through and shared among a large number of atoms (10^{10} or more) with no big change in temperature. When there are only 500 atoms, however, the substrate is almost immediately vaporized by the deposition. Something similar happens in biophysical simulations. The temperature of the system in NVE is naturally raised when macromolecules such as proteins undergo exothermic conformational changes and binding.

Canonical ensemble (NVT)

In the canonical ensemble, moles (N), volume (V) and temperature (T) are conserved. It is also sometimes called constant temperature molecular dynamics (CTMD). In NVT, the energy of endothermic and exothermic processes is exchanged with a thermostat.

A variety of thermostat methods are available to add and remove energy from the boundaries of an MD system in a realistic way, approximating the canonical ensemble. Popular techniques to control temperature include the Nosé-Hoover thermostat, the Berendsen thermostat, and Langevin dynamics. Note that the Berendsen thermostat might introduce the flying ice cube effect, which leads to unphysical translations and rotations of the simulated system.

Isothermal-Isobaric (NPT) ensemble

In the isothermal-isobaric ensemble, moles (N), pressure (P) and temperature (T) are conserved. In addition to a thermostat, a barostat is needed. It corresponds most closely to laboratory conditions with a flask open to ambient temperature and pressure.

In the simulation of biological membranes, isotropic pressure control is not appropriate. For lipid bilayers, pressure control occurs under constant membrane area (NPAT) or constant surface tension "gamma" (NPγT).

Generalized ensembles

The replica exchange method is a generalized ensemble. It was originally created to deal with the slow dynamics of disordered spin systems. It is also called parallel tempering. The replica exchange MD (REMD) formulation [9] tries to overcome the multiple-minima problem by exchanging the temperature of non-interacting replicas of the system running at several temperatures.

Potentials in MD simulations

A molecular dynamics simulation requires the definition of a potential function, or a description of the terms by which the particles in the simulation will interact. In chemistry and biology this is usually referred to as a force field. Potentials may be defined at many levels of physical accuracy; those most commonly used in chemistry are based on molecular mechanics and embody a classical treatment of particle-particle interactions that can reproduce structural and conformational changes but usually cannot reproduce chemical reactions.

The reduction from a fully quantum description to a classical potential entails two main approximations. The first one is the Born-Oppenheimer approximation, which states that the dynamics of electrons is so fast that they can be considered to react instantaneously to the motion of their nuclei. As a consequence, they may be treated separately. The second one treats the nuclei, which are much heavier than electrons, as point particles that follow classical Newtonian dynamics. In classical molecular dynamics the effect of the electrons is approximated as a single potential energy surface, usually representing the ground state.

When finer levels of detail are required, potentials based on quantum mechanics are used; some techniques attempt to create hybrid classical/quantum potentials where the bulk of the system is treated classically but a small region is treated as a quantum system, usually undergoing a chemical transformation.

Empirical potentials

Empirical potentials used in chemistry are frequently called force fields, while those used in materials physics are called just empirical or analytical potentials.

Most force fields in chemistry are empirical and consist of a summation of bonded forces associated with chemical bonds, bond angles, and bond dihedrals, and non-bonded forces associated with van der Waals forces and electrostatic charge. Empirical potentials represent quantum-mechanical effects in a limited way through ad-hoc functional approximations. These potentials contain free parameters such as atomic charge, van der Waals parameters reflecting estimates of atomic radius, and equilibrium bond length, angle, and dihedral; these are obtained by fitting against detailed electronic calculations

(quantum chemical simulations) or experimental physical properties such as elastic constants, lattice parameters and spectroscopic measurements.

Because of the non-local nature of non-bonded interactions, they involve at least weak interactions between all particles in the system. Its calculation is normally the bottleneck in the speed of MD simulations. To lower the computational cost, force fields employ numerical approximations such as shifted cutoff radii, reaction field algorithms, particle mesh Ewald summation, or the newer Particle-Particle Particle Mesh (P3M).

Chemistry force fields commonly employ preset bonding arrangements (an exception being *ab-initio* dynamics), and thus are unable to model the process of chemical bond breaking and reactions explicitly. On the other hand, many of the potentials used in physics, such as those based on the bond order formalism can describe several different coordinations of a system and bond breaking. Examples of such potentials include the Brenner potential[10] for hydrocarbons and its further developments for the C-Si-H and C-O-H systems. The ReaxFF potential[11] can be considered a fully reactive hybrid between bond order potentials and chemistry force fields.

Pair potentials vs.many-body potentials

The potential functions representing the non-bonded energy are formulated as a sum over interactions between the particles of the system. The simplest choice, employed in many popular force fields, is the "pair potential", in which the total potential energy can be calculated from the sum of energy contributions between pairs of atoms. An example of such a pair potential is the non-bonded Lennard-Jones potential (also known as the 6-12 potential), used for calculating van der Waals forces.

$$U(r) = 4\varepsilon \left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^{6} \right]$$

Another example is the Born (ionic) model of the ionic lattice. The first term in the next equation is Coulomb's law for a pair of ions, the second term is the short-range repulsion explained by Pauli's exclusion principle and the final term is the dispersion interaction term. Usually, a simulation only includes the dipolar term, although sometimes the quadrupolar term is included as well.

$$U_{ij}(r_{ij}) = \sum \frac{z_i z_j}{4\pi\epsilon_0} \frac{1}{r_{ij}} + \sum A_l \exp \frac{-r_{ij}}{p_l} + \sum C_l r_{ij}^{-n_j} + \cdots$$

In many-body potentials, the potential energy includes the effects of three or more particles interacting with each other. In simulations with pairwise potentials, global interactions in the system also exist, but they occur only through pairwise terms. In many-body potentials, the potential energy cannot be found by a sum over pairs of atoms, as these interactions are calculated explicitly as a combination of higher-order terms. In the statistical view, the dependency between the variables cannot in general be expressed using only pairwise products of the degrees of freedom. For example, the Tersoff potential[12] , which was originally used to simulate carbon, silicon and germanium and has since been used for a wide range of other materials, involves a sum over groups of three atoms, with the angles between the atoms being an important factor in the potential. Other examples are the embedded-atom method (EAM)[13] and the Tight-Binding Second Moment Approximation (TBSMA) potentials[14] , where the electron density of states in the region of an atom is calculated from a sum of contributions from surrounding atoms, and the potential energy contribution is then a function of this sum.

Semi-empirical potentials

Semi-empirical potentials make use of the matrix representation from quantum mechanics. However, the values of the matrix elements are found through empirical formulae that estimate the degree of overlap of specific atomic orbitals. The matrix is then diagonalized to determine the occupancy of the different atomic orbitals, and empirical formulae are used once again to determine the energy contributions of the orbitals.

There are a wide variety of semi-empirical potentials, known as tight-binding potentials, which vary according to the atoms being modeled.

Polarizable potentials

Most classical force fields implicitly include the effect of polarizability, e.g. by scaling up the partial charges obtained from quantum chemical calculations. These partial charges are stationary with respect to the mass of the atom. But molecular dynamics simulations can explicitly model polarizability with the introduction of induced dipoles through different methods, such as Drude particles or fluctuating charges. This allows for a dynamic redistribution of charge between atoms which responds to the local chemical environment.

For many years, polarizable MD simulations have been touted as the next generation. For homogenous liquids such as water, increased accuracy has been achieved through the inclusion of polarizability.[15] Some promising results have also been achieved for proteins.[16] However, it is still uncertain how to best approximate polarizability in a simulation.

Ab-initio methods

In classical molecular dynamics, a single potential energy surface (usually the ground state) is represented in the force field. This is a consequence of the Born-Oppenheimer approximation. If excited states, chemical reactions or a more accurate representation is needed, electronic behavior can be obtained from first principles by using a quantum mechanical method, such as Density Functional Theory. This is known as Ab Initio Molecular Dynamics (AIMD). Due to the cost of treating the electronic degrees of freedom, the computational cost of this simulations is much higher than classical molecular dynamics. This implies that AIMD is limited to smaller systems and shorter periods of time.

Ab-initio → quantum-mechanical methods may be used to calculate the potential energy of a system on the fly, as needed for conformations in a trajectory. This calculation is usually made in the close neighborhood of the reaction coordinate. Although various approximations may be used, these are based on theoretical considerations, not on empirical fitting. *Ab-Initio* calculations produce a vast amount of information that is not available from empirical methods, such as density of electronic states or other electronic properties. A significant advantage of using *ab-initio* methods is the ability to study reactions that involve breaking or formation of covalent bonds, which correspond to multiple electronic states.

A popular software for *ab-initio* molecular dynamics is the Car-Parrinello Molecular Dynamics (CPMD) package based on the density functional theory.

Hybrid QM/MM

QM (quantum-mechanical) methods are very powerful. However, they are computationally expensive, while the MM (classical or molecular mechanics) methods are fast but suffer from several limitations (require extensive parameterization; energy estimates obtained are not very accurate; cannot be used to simulate reactions where covalent bonds are broken/formed; and are limited in their abilities for providing accurate details regarding the chemical environment). A new class of method has emerged that combines the good points of QM (accuracy) and MM (speed) calculations. These methods are known as mixed or hybrid quantum-mechanical and molecular mechanics methods (hybrid QM/MM). The methodology for such techniques was introduced by Warshel and coworkers. In the recent years have been pioneered by several groups including: Arieh Warshel (University of Southern California), Weitao Yang (Duke University), Sharon Hammes-Schiffer (The Pennsylvania State University), Donald Truhlar and Jiali Gao (University of Minnesota) and Kenneth Merz (University of Florida).

The most important advantage of hybrid QM/MM methods is the speed. The cost of doing classical molecular dynamics (MM) in the most straightforward case scales $O(n^2)$, where N is the number of atoms in the system. This is mainly due to electrostatic interactions term (every particle interacts with every other particle). However, use of cutoff radius, periodic pair-list updates and more recently the variations of the particle-mesh Ewald's (PME) method has reduced this between O(N) to $O(n^2)$. In other words, if a system with twice many atoms is simulated then it would take between twice to four times as much computing power. On the other hand the simplest *ab-initio* calculations typically scale $O(n^3)$ or worse (Restricted Hartree-Fock calculations have been suggested to scale $\sim O(n^{2.7})$). To overcome the limitation, a small part of the system is treated quantum-mechanically (typically active-site of an enzyme) and the remaining system is treated classically.

In more sophisticated implementations, QM/MM methods exist to treat both light nuclei susceptible to quantum effects (such as hydrogens) and electronic states. This allows generation of hydrogen wave-functions (similar to electronic wave-functions). This methodology has been useful in investigating phenomenon such as hydrogen tunneling. One example where QM/MM methods have provided new discoveries is the calculation of hydride transfer in the enzyme liver alcohol dehydrogenase. In this case, tunneling is important for the hydrogen, as it determines the reaction rate.[17]

Coarse-graining and reduced representations

At the other end of the detail scale are coarse-grained and lattice models. Instead of explicitly representing every atom of the system, one uses "pseudo-atoms" to represent groups of atoms. MD simulations on very large systems may require such large computer resources that they cannot easily be studied by traditional all-atom methods. Similarly, simulations of processes on long timescales (beyond about 1 microsecond) are prohibitively expensive, because they require so many timesteps. In these cases, one can sometimes tackle the problem by using reduced representations, which are also called coarse-grained models.

Examples for coarse graining (CG) methods are discontinuous molecular dynamics (CG-DMD)[18] [19] and Go-models[20] . Coarse-graining is done sometimes taking larger pseudo-atoms. Such united atom approximations have been used in MD simulations of biological membranes. The aliphatic tails of lipids are represented by a few pseudo-atoms

by gathering 2-4 methylene groups into each pseudo-atom.

The parameterization of these very coarse-grained models must be done empirically, by matching the behavior of the model to appropriate experimental data or all-atom simulations. Ideally, these parameters should account for both enthalpic and entropic contributions to free energy in an implicit way. When coarse-graining is done at higher levels, the accuracy of the dynamic description may be less reliable. But very coarse-grained models have been used successfully to examine a wide range of questions in structural biology.

Examples of applications of coarse-graining in biophysics:

- protein folding studies are often carried out using a single (or a few) pseudo-atoms per amino acid;
- DNA supercoiling has been investigated using 1-3 pseudo-atoms per basepair, and at even lower resolution;
- Packaging of double-helical DNA into bacteriophage has been investigated with models where one pseudo-atom represents one turn (about 10 basepairs) of the double helix;
- RNA structure in the ribosome and other large systems has been modeled with one pseudo-atom per nucleotide.

The simplest form of coarse-graining is the "united atom" (sometimes called "extended atom") and was used in most early MD simulations of proteins, lipids and nucleic acids. For example, instead of treating all four atoms of a CH_3 methyl group explicitly (or all three atoms of CH_2 methylene group), one represents the whole group with a single pseudo-atom. This pseudo-atom must, of course, be properly parameterized so that its van der Waals interactions with other groups have the proper distance-dependence. Similar considerations apply to the bonds, angles, and torsions in which the pseudo-atom participates. In this kind of united atom representation, one typically eliminates all explicit hydrogen atoms except those that have the capability to participate in hydrogen bonds ("polar hydrogens"). An example of this is the Charmm 19 force-field.

The polar hydrogens are usually retained in the model, because proper treatment of hydrogen bonds requires a reasonably accurate description of the directionality and the electrostatic interactions between the donor and acceptor groups. A hydroxyl group, for example, can be both a hydrogen bond donor and a hydrogen bond acceptor, and it would be impossible to treat this with a single OH pseudo-atom. Note that about half the atoms in a protein or nucleic acid are nonpolar hydrogens, so the use of united atoms can provide a substantial savings in computer time.

Examples of applications

Molecular dynamics is used in many fields of science.

- First macromolecular MD simulation published (1977, Size: 500 atoms, Simulation Time: 9.2 ps=0.0092 ns, Program: CHARMM precursor) Protein: Bovine Pancreatic Trypsine Inhibitor. This is one of the best studied proteins in terms of folding and kinetics. Its simulation published in Nature magazine paved the way for understanding protein motion as essential in function and not just accessory.[21]
- MD is the standard method to treat collision cascades in the heat spike regime, i.e. the effects that energetic neutron and ion irradiation have on solids an solid surfaces.[22] [23]

The following two biophysical examples are not run-of-the-mill MD simulations. They illustrate almost heroic efforts to produce simulations of a system of very large size (a complete virus) and very long simulation times (500 microseconds):

- MD simulation of the complete satellite tobacco mosaic virus (**STMV**) (2006, Size: 1 million atoms, Simulation time: 50 ns, program: NAMD) This virus is a small, icosahedral plant virus which worsens the symptoms of infection by Tobacco Mosaic Virus (TMV). Molecular dynamics simulations were used to probe the mechanisms of viral assembly. The entire STMV particle consists of 60 identical copies of a single protein that make up the viral capsid (coating), and a 1063 nucleotide single stranded RNA genome. One key finding is that the capsid is very unstable when there is no RNA inside. The simulation would take a single 2006 desktop computer around 35 years to complete. It was thus done in many processors in parallel with continuous communication between them.[24]
- Folding Simulations of the Villin Headpiece in All-Atom Detail (2006, Size: 20,000 atoms; Simulation time: 500 μs = 500,000 ns, Program: folding@home) This simulation was run in 200,000 CPU's of participating personal computers around the world. These computers had the folding@home program installed, a large-scale distributed computing effort coordinated by Vijay Pande at Stanford University. The kinetic properties of the Villin Headpiece protein were probed by using many independent, short trajectories run by CPU's without continuous real-time communication. One technique employed was the Pfold value analysis, which measures the probability of folding before unfolding of a specific starting conformation. Pfold gives information about transition state structures and an ordering of conformations along the folding pathway. Each trajectory in a Pfold calculation can be relatively short, but many independent trajectories are needed.[25]

Molecular dynamics algorithms

Integrators

- Verlet-Stoermer integration
- Runge-Kutta integration
- Beeman's algorithm
- Gear predictor - corrector
- Constraint algorithms (for constrained systems)
- Symplectic integrator

Short-range interaction algorithms

- Cell lists
- Verlet list
- Bonded interactions

Long-range interaction algorithms

- Ewald summation
- Particle Mesh Ewald (PME)
- Particle-Particle Particle Mesh P3M
- Reaction Field Method

Parallelization strategies

- Domain decomposition method (Distribution of system data for parallel computing)
- Molecular Dynamics - Parallel Algorithms [26]

Major software for MD simulations

- Abalone (classical, implicit water)
- ABINIT (DFT)
- ACEMD [27] (running on NVIDIA GPUs: heavily optimized with CUDA)
- ADUN [28] (classical, P2P database for simulations)
- AMBER (classical)
- Ascalaph [29] (classical, GPU accelerated)
- CASTEP (DFT)
- CPMD (DFT)
- CP2K [30] (DFT)
- CHARMM (classical, the pioneer in MD simulation, extensive analysis tools)
- COSMOS [31] (classical and hybrid QM/MM, quantum-mechanical atomic charges with BPT)
- Desmond [32] (classical, parallelization with up to thousands of CPU's)
- DL_POLY [33] (classical)
- ESPResSo (classical, coarse-grained, parallel, extensible)
- Fireball [34] (tight-binding DFT)
- GROMACS (classical)
- GROMOS (classical)
- GULP (classical)
- Hippo [35] (classical)
- LAMMPS (classical, large-scale with spatial-decomposition of simulation domain for parallelism)
- MDynaMix (classical, parallel)
- MOLDY [36] (classical, parallel) latest release [37]
- Materials Studio [38] (Forcite MD using COMPASS, Dreiding, Universal, cvff and pcff forcefields in serial or parallel, QMERA (QM+MD), ONESTEP (DFT), etc.)
- MOSCITO (classical)
- NAMD (classical, parallelization with up to thousands of CPU's)
- NEWTON-X [39] (ab initio, surface-hopping dynamics)
- ProtoMol [40] (classical, extensible, includes multigrid electrostatics)
- PWscf (DFT)
- S/PHI/nX [41] (DFT)
- SIESTA (DFT)
- VASP (DFT)
- TINKER (classical)
- YASARA [42] (classical)
- ORAC [43] (classical)
- XMD (classical)

Related software

- VMD - MD simulation trajectories can be visualized and analyzed.
- PyMol - Molecular Visualization software written in python
- Packmol [44] Package for building starting configurations for MD in an automated fashion
- Sirius - Molecular modeling, analysis and visualization of MD trajectories
- esra [45] - Lightweight molecular modeling and analysis library (Java/Jython/Mathematica).
- Molecular Workbench [46] - Interactive molecular dynamics simulations on your desktop
- BOSS - MC in OPLS

Specialized hardware for MD simulations

- Anton - A specialized, massively parallel supercomputer designed to execute MD simulations.
- MDGRAPE - A special purpose system built for molecular dynamics simulations, especially protein structure prediction.

See also

- → Molecular graphics
- Molecular modeling
- Computational chemistry
- Energy drift
- Force field in Chemistry
- Force field implementation
- → Monte Carlo method
- Molecular Design software
- Molecular mechanics
- Molecular modeling on GPU
- Protein dynamics
- Implicit solvation
- Car-Parrinello method
- Symplectic numerical integration
- Software for molecular mechanics modeling
- Dynamical systems
- Theoretical chemistry
- → Statistical mechanics
- → Quantum chemistry
- Discrete element method
- List of nucleic acid simulation software

References

[1] Alder, B. J.; T. E. Wainwright (1959). "Studies in Molecular Dynamics. I. General Method". *J. Chem. Phys.* **31** (2): 459. doi: 10.1063/1.1730376 (http://dx.doi.org/10.1063/1.1730376).

[2] A. Rahman (1964). "Correlations in the Motion of Atoms in Liquid Argon". *Phys Rev* **136**: A405-A411. doi: 10.1103/PhysRev.136.A405 (http://dx.doi.org/10.1103/PhysRev.136.A405).

[3] Bernal, J.D. (1964). "The Bakerian lecture, 1962: The structure of liquids". *Proc. R. Soc.* **280**: 299–322. doi: 10.1098/rspa.1964.0147 (http://dx.doi.org/10.1098/rspa.1964.0147).

[4] Schlick, T. (1996). "Pursuing Laplace's Vision on Modern Computers". in J. P. Mesirov, K. Schulten and D. W. Sumners. *Mathematical Applications to Biomolecular Structure and Dynamics, IMA Volumes in Mathematics and Its Applications*. **82**. New York: Springer-Verlag. pp. 218–247. ISBN 978-0387948386.

[5] de Laplace, P. S. (1820) (in French). *Oeuveres Completes de Laplace, Theorie Analytique des Probabilites*. Paris, France: Gauthier-Villars.

[6] Streett WB, Tildesley DJ, Saville G (1978). "Multiple time-step methods in molecular dynamics". *Mol Phys* **35** (3): 639-648. doi: 10.1080/00268977800100471 (http://dx.doi.org/10.1080/00268977800100471).

[7] Tuckerman ME, Berne BJ, Martyna GJ (1991). "Molecular dynamics algorithm for multiple time scales: systems with long range forces". *J Chem Phys* **94** (10): 6811-6815.

[8] Tuckerman ME, Berne BJ, Martyna GJ (1992). "Reversible multiple time scale molecular dynamics". *J Chem Phys* **97** (3): 1990-2001. doi: 10.1063/1.463137 (http://dx.doi.org/10.1063/1.463137).

[9] Sugita, Yuji; Yuko Okamoto (1999). "Replica-exchange molecular dynamics method for protein folding". *Chem Phys Letters* **314**: 141–151. doi: 10.1016/S0009-2614(99)01123-9 (http://dx.doi.org/10.1016/S0009-2614(99)01123-9).

[10] Brenner, D. W. (1990). "Empirical potential for hydrocarbons for use in simulating the chemical vapor deposition of diamond films". *Phys. Rev. B* **42** (15): 9458. doi: 10.1103/PhysRevB.42.9458 (http://dx.doi.org/10.1103/PhysRevB.42.9458).

[11] van Duin, A.; Siddharth Dasgupta, Francois Lorant and William A. Goddard III (2001). *J. Phys. Chem. A* **105**: 9398.

[12] Tersoff, J. (1989). ""Modeling solid-state chemistry: Interatomic potentials for multicomponent systems". *Phys. Rev. B* **39**: 5566. doi: 10.1103/PhysRevB.39.5566 (http://dx.doi.org/10.1103/PhysRevB.39.5566).

[13] Daw, M. S.; S. M. Foiles and M. I. Baskes (1993). "The embedded-atom method: a review of theory and applications". *Mat. Sci. And Engr. Rep.* **9**: 251. doi: 10.1016/0920-2307(93)90001-U (http://dx.doi.org/10.1016/0920-2307(93)90001-U).

[14] Cleri, F.; V. Rosato (1993). "Tight-binding potentials for transition metals and alloys". *Phys. Rev. B* **48**: 22. doi: 10.1103/PhysRevB.48.22 (http://dx.doi.org/10.1103/PhysRevB.48.22).

[15] Lamoureux G, Harder E, Vorobyov IV, Roux B, MacKerell AD (2006). "A polarizable model of water for molecular dynamics simulations of biomolecules". *Chem Phys Lett* **418**: 245-249. doi: 10.1016/j.cplett.2005.10.135 (http://dx.doi.org/10.1016/j.cplett.2005.10.135).

[16] Patel, S.; MacKerell, Jr. AD; Brooks III, Charles L (2004). "CHARMM fluctuating charge force field for proteins: II protein/solvent properties from molecular dynamics simulations using a nonadditive electrostatic model". *J Comput Chem* **25**: 1504–1514. doi: 10.1002/jcc.20077 (http://dx.doi.org/10.1002/jcc.20077).

[17] Billeter, SR; SP Webb, PK Agarwal, T Iordanov, S Hammes-Schiffer (2001). "Hydride Transfer in Liver Alcohol Dehydrogenase: Quantum Dynamics, Kinetic Isotope Effects, and Role of Enzyme Motion". *J Am Chem Soc* **123**: 11262–11272. doi: 10.1021/ja011384b (http://dx.doi.org/10.1021/ja011384b).

[18] Smith, A; CK Hall (2001). "Alpha-Helix Formation: Discontinuous Molecular Dynamics on an Intermediate-Resolution Protein Model". *Proteins* **44**: 344-360.

[19] Ding, F; JM Borreguero, SV Buldyrey, HE Stanley, NV Dokholyan (2003). "Mechanism for the alpha-helix to beta-hairpin transition". *J Am Chem Soc* **53**: 220–228. doi: 10.1002/prot.10468 (http://dx.doi.org/10.1002/prot.10468).

[20] Paci, E; M Vendruscolo, M Karplus (2002). "Validity of Go Models: Comparison with a Solvent-Shielded Empirical Energy Decomposition". *Biophys J* **83**: 3032–3038. doi: 10.1016/S0006-3495(02)75308-3 (http://dx.doi.org/10.1016/S0006-3495(02)75308-3).

[21] McCammon, J; JB Gelin, M Karplus (1977). "Dynamics of folded proteins". *Nature* **267**: 585–590. doi: 10.1038/267585a0 (http://dx.doi.org/10.1038/267585a0).

[22] Averback, R. S.; Diaz de la Rubia, T. (1998). "Displacement damage in irradiated metals and semiconductors". in H. Ehrenfest and F. Spaepen. *Solid State Physics*. **51**. New York: Academic Press. p. 281-402.

[23] R. Smith, ed (1997). *Atomic & ion collisions in solids and at surfaces: theory, simulation and applications*. Cambridge, UK: Cambridge University Press.

[24] Freddolino P, Arkhipov A, Larson SB, McPherson A, Schulten K. "Molecular dynamics simulation of the Satellite Tobacco Mosaic Virus (STMV)" (http://www.ks.uiuc.edu/Research/STMV/). *Theoretical and*

Computational Biophysics Group. University of Illinois at Urbana Champaign. .
[25] The Folding@Home Project (http://folding.stanford.edu/) and recent papers (http://folding.stanford.edu/papers.html) published using trajectories from it. Vijay Pande Group. Stanford University
[26] http://www.cs.sandia.gov/~sjplimp/md.html
[27] http://www.acellera.com/index.php?arg=acemd
[28] http://cbbl.imim.es/Adun
[29] http://www.agilemolecule.com/Products.html
[30] http://cp2k.berlios.de/
[31] http://www.cosmos-software.de/ce_intro.html
[32] http://www.DEShawResearch.com/resources.html
[33] http://www.ccp5.ac.uk/DL_POLY/
[34] http://fireball-dft.org
[35] http://www.biowerkzeug.com/
[36] http://www.ccp5.ac.uk/moldy/moldy.html
[37] http://ccpforge.cse.rl.ac.uk/frs/?group_id=34
[38] http://accelrys.com/products/materials-studio/
[39] http://www.univie.ac.at/newtonx/
[40] http://protomol.sourceforge.net/
[41] http://www.sphinxlib.de
[42] http://www.yasara.org
[43] http://www.chim.unifi.it/orac/
[44] http://www.ime.unicamp.br/~martinez/packmol
[45] http://esra.sourceforge.net/cgi-bin/index.cgi
[46] http://mw.concord.org/modeler/

General references

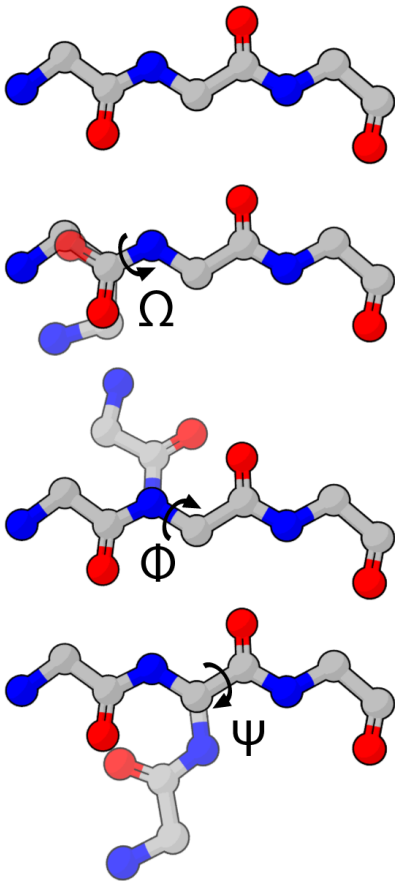
- M. P. Allen, D. J. Tildesley (1989) Computer simulation of liquids. Oxford University Press. ISBN 0-19-855645-4.
- J. A. McCammon, S. C. Harvey (1987) Dynamics of Proteins and Nucleic Acids. Cambridge University Press. ISBN 0521307503 (hardback).
- D. C. Rapaport (1996) The Art of Molecular Dynamics Simulation. ISBN 0-521-44561-2.
- Frenkel, Daan; Smit, Berend (2002) [2001]. *Understanding Molecular Simulation : from algorithms to applications*. San Diego, California: Academic Press. ISBN 0-12-267351-4.
- J. M. Haile (2001) Molecular Dynamics Simulation: Elementary Methods. ISBN 0-471-18439-X
- R. J. Sadus, *Molecular Simulation of Fluids: Theory, Algorithms and Object-Orientation*, 2002, ISBN 0-444-51082-6
- Oren M. Becker, Alexander D. Mackerell Jr, Benoît Roux, Masakatsu Watanabe (2001) Computational Biochemistry and Biophysics. Marcel Dekker. ISBN 0-8247-0455-X.
- Andrew Leach (2001) Molecular Modelling: Principles and Applications. (2nd Edition) Prentice Hall. ISBN 978-0582382107.
- Tamar Schlick (2002) Molecular Modeling and Simulation. Springer. ISBN 0-387-95404-X.
- William Graham Hoover (1991) Computational Statistical Mechanics, Elsevier, ISBN 0-444-88192-1.

External links

- The Blue Gene Project (http://researchweb.watson.ibm.com/bluegene/) (IBM)
- D. E. Shaw Research (http://deshawresearch.com/) (D. E. Shaw Research)
- Molecular Physics (http://www.tandf.co.uk/journals/titles/00268976.asp)
- Statistical mechanics of Nonequilibrium Liquids (http://www.phys.unsw.edu.au/~gary/book.html) Lecture Notes on non-equilibrium MD
- Introductory Lecture on Classical Molecular Dynamics (http://www.fz-juelich.de/nic-series/volume10/sutmann.pdf) by Dr. Godehard Sutmann, NIC, Forschungszentrum Jülich, Germany
- Introductory Lecture on Ab Initio Molecular Dynamics and Ab Initio Path Integrals (http://www.fz-juelich.de/nic-series/volume10/tuckerman2.pdf) by Mark E. Tuckerman, New York University, USA
- Introductory Lecture on Ab initio molecular dynamics: Theory and Implementation (http://www.fz-juelich.de/nic-series/Volume1/marx.pdf) by Dominik Marx, Ruhr-Universität Bochum and Jürg Hutter, Universität Zürich
- Atomic-scale Friction Research and Education Synergy Hub (AFRESH) (http://nsfafresh.org) an Engineering Virtual Organization for the atomic-scale friction community to share, archive, link, and discuss data, knowledge and tools related to atomic-scale friction.
  - AFRESH (http://nsfafresh.org/wiki/index.php?title=Computational_Tribology) also provides detailed information regarding computational methods such as Molecular Dynamics as it relates to atomic-scale friction research.

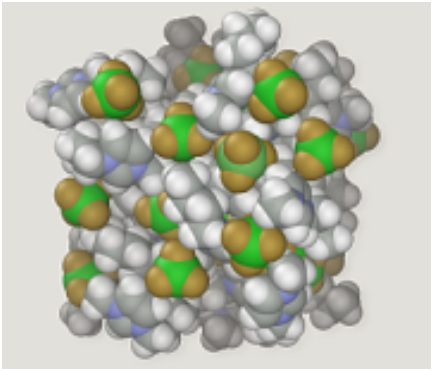
Molecular modelling

Molecular modelling is a collective term that refers to theoretical methods and computational techniques to model or mimic the behaviour of molecules. The techniques are used in the fields of computational chemistry, computational biology and materials science for studying molecular systems ranging from small chemical systems to large biological molecules and material assemblies. The simplest calculations can be performed by hand, but inevitably computers are required to perform molecular modelling of any reasonably sized system. The common feature of molecular modelling techniques is the atomistic level description of the molecular systems; the lowest level of information is individual atoms (or a small group of atoms). This is in contrast to → quantum chemistry (also known as electronic structure calculations) where electrons are considered explicitly. The benefit of molecular modelling is that it reduces the complexity of the system, allowing many more particles (atoms) to be considered during simulations.



The backbone dihedral angles are included in the molecular model of a protein.

Molecular mechanics is one aspect of molecular modelling, as it is refers to the use of classical mechanics/Newtonian mechanics to describe the physical basis behind the models. Molecular models typically describe atoms (nucleus and electrons collectively) as point charges with an associated mass. The interactions between neighbouring atoms are described by spring-like interactions (representing chemical bonds) and van der Waals forces. The Lennard-Jones potential is commonly used to describe van der Waals forces. The electrostatic interactions are computed based on Coulomb's law. Atoms are assigned coordinates in Cartesian space or in internal coordinates, and can also be assigned velocities in dynamical simulations. The atomic velocities are related to the temperature of the system, a macroscopic quantity. The collective mathematical expression is known as a potential function and is related to the system internal energy (U), a thermodynamic quantity equal to the sum of potential and kinetic energies. Methods which minimize the potential energy are known as energy minimization techniques (e.g., steepest descent and conjugate gradient), while methods that model the behaviour of the system with propagation of time are known as → molecular dynamics.


Modelling of ionic liquid

$$E = E_{bonds} + E_{angle} + E_{dihedral} + E_{non-bonded}$$

$$E_{non-bonded} = E_{electrostatic} + E_{vanderWaals}$$

This function, referred to as a potential function, computes the molecular potential energy as a sum of energy terms that describe the deviation of bond lengths, bond angles and torsion angles away from equilibrium values, plus terms for non-bonded pairs of atoms describing van der Waals and electrostatic interactions. The set of parameters consisting of equilibrium bond lengths, bond angles, partial charge values, force constants and van der Waals parameters are collectively known as a force field. Different implementations of molecular mechanics use slightly different mathematical expressions, and therefore, different constants for the potential function. The common force fields in use today have been developed by using high level quantum calculations and/or fitting to experimental data. The technique known as energy minimization is used to find positions of zero gradient for all atoms, in other words, a local energy minimum. Lower energy states are more stable and are commonly investigated because of their role in chemical and biological processes. A → molecular dynamics simulation, on the other hand, computes the behaviour of a system as a function of time. It involves solving Newton's laws of motion, principally the second law, **F = ma**. Integration of Newton's laws of motion, using different integration algorithms, leads to atomic trajectories in space and time. The force on an atom is defined as the negative gradient of the potential energy function. The energy minimization technique is useful for obtaining a static picture for comparing between states of similar systems, while molecular dynamics provides information about the dynamic processes with the intrinsic inclusion of temperature effects.

Molecules can be modelled either in vacuum or in the presence of a solvent such as water. Simulations of systems in vacuum are referred to as *gas-phase* simulations, while those that include the presence of solvent molecules are referred to as *explicit solvent* simulations. In another type of simulation, the effect of solvent is estimated using an empirical mathematical expression; these are known as *implicit solvation* simulations.

Molecular modelling methods are now routinely used to investigate the structure, dynamics and thermodynamics of inorganic, biological, and polymeric systems. The types of biological activity that have been investigated using molecular modelling include protein folding, enzyme catalysis, protein stability, conformational changes associated with biomolecular function, and molecular recognition of proteins, DNA, and membrane complexes.

Popular software for molecular modelling

- Abalone
- AMBER
- ADF
- Ascalaph Designer[1]
- BALLView
- Biskit
- BOSS
- Cerius2
- Chimera
- CHARMM
- Coot (program)[2] for X-ray crystallography of biological molecules
- COSMOS (software)[3]

- CP2K
- CPMD
- Firefly
- GAMESS (UK)
- GAMESS (US)
- GAUSSIAN
- Ghemical
- GROMACS
- GROMOS
- InsightII
- LAMMPS
- MacroModel
- MarvinSpace[4]
- Materials Studio
- MDynaMix
- MMTK
- MOE (software)[5]
- Molecular Docking Server
- Molsoft ICM[6]
- MOPAC
- NAMD
- NOCH
- Oscail X
- PyMOL
- Q-Chem
- Sirius
- SPARTAN (software)[7]
- STR3DI32[8]
- Sybyl (software)[9]
- MCCCS Towhee[10]
- TURBOMOLE
- ReaxFF
- VMD
- WHAT IF[11]
- xeo[12]
- YASARA[13]
- Zodiac (software)[14]

See also

- Cheminformatics
- Computational chemistry
- Density functional theory programs.
- Force field in Chemistry
- Force field implementation
- List of nucleic acid simulation software
- List of protein structure prediction software
- Molecular Design software
- → Molecular dynamics
- → Molecular graphics
- Molecular mechanics
- Molecular model
- Molecular modelling on GPU
- Molecule editor
- → Monte Carlo method
- Quantum chemistry computer programs
- Semi-empirical quantum chemistry method
- Software for molecular mechanics modelling
- Structural Bioinformatics

External links

- Center for Molecular Modeling at the National Institutes of Health (NIH) [15] (U.S. Government Agency)
- Molecular Simulation [16], details for the Molecular Simulation journal, ISSN: 0892-7022 (print), 1029-0435 (online)
- The eCheminfo [17] Network and Community of Practice in Informatics and Modeling

References

- M. P. Allen, D. J. Tildesley, *Computer simulation of liquids*, 1989, Oxford University Press, ISBN 0-19-855645-4.
- A. R. Leach, *Molecular Modelling: Principles and Applications*, 2001, ISBN 0-582-38210-6
- D. Frenkel, B. Smit, *Understanding Molecular Simulation: From Algorithms to Applications*, 1996, ISBN 0-12-267370-0
- D. C. Rapaport, *The Art of Molecular Dynamics Simulation*, 2004, ISBN 0-521-82586-7
- R. J. Sadus, *Molecular Simulation of Fluids: Theory, Algorithms and Object-Orientation*, 2002, ISBN 0-444-51082-6
- K.I.Ramachandran, G Deepa and Krishnan Namboori. P.K. *Computational Chemistry and Molecular Modeling Principles and Applications* 2008[18] ISBN 978-3-540-77302-3 Springer-Verlag GmbH

Homepage

[1] *Agile Molecule (http://www.agilemolecule.com/index.html)*
[2] *York Structural Biology Laboratory (http://www.ysbl.york.ac.uk/~emsley/coot/)*
[3] COSMOS (http://www.cosmos-software.de/ce_intro.html) - **C**omputer **S**imulation of **Mo**lecular **S**tructures
[4] *ChemAxon (http://www.chemaxon.com/product/mspace.html)*
[5] MOE - **M**olecular **O**perating **E**nvironment, *Chemical Computing Group (http://www.chemcomp.com/)*
[6] *Molsoft (http://www.molsoft.com/)*
[7] *Wavefunction, Inc. (http://www.wavefun.com/)*
[8] *Exorga, Inc. (http://www.exorga.com/)*
[9] *Tipos (http://www.tripos.com/sybyl/)*
[10] *MCCCS Towhee (http://towhee.sourceforge.net/)* - **M**onte **C**arlo for **C**omplex **C**hemical **S**ystems
[11] *CMBI (http://swift.cmbi.ru.nl/whatif/)*
[12] *xeo (http://sourceforge.net/projects/xeo)*
[13] *YASARA (http://www.yasara.org/)*
[14] *ZedeN (http://www.zeden.org)*
[15] http://cmm.info.nih.gov/modeling/
[16] http://www.tandf.co.uk/journals/titles/08927022.asp
[17] http://www.echeminfo.com/
[18] http://www.amrita.edu/cen/ccmm

Monte Carlo method

Monte Carlo methods are a class of computational algorithms that rely on repeated random sampling to compute their results. Monte Carlo methods are often used when simulating physical and mathematical systems. Because of their reliance on repeated computation and random or pseudo-random numbers, Monte Carlo methods are most suited to calculation by a computer. Monte Carlo methods tend to be used when it is unfeasible or impossible to compute an exact result with a deterministic algorithm.[1]

Monte Carlo simulation methods are especially useful in studying systems with a large number of coupled degrees of freedom, such as fluids, disordered materials, strongly coupled solids, and cellular structures (see cellular Potts model). More broadly, Monte Carlo methods are useful for modeling phenomena with significant uncertainty in inputs, such as the calculation of risk in business. These methods are also widely used in mathematics: a classic use is for the evaluation of definite integrals, particularly multidimensional integrals with complicated boundary conditions. It is a widely successful method in risk analysis when compared to alternative methods or human intuition. When Monte Carlo simulations have been applied in space exploration and oil exploration, actual observations of failures, cost overruns and schedule overruns are routinely better predicted by the simulations than by human intuition or alternative "soft" methods.[2]

The term "Monte Carlo method" was coined in the 1940s by physicists working on nuclear weapon projects in the Los Alamos National Laboratory.[3]

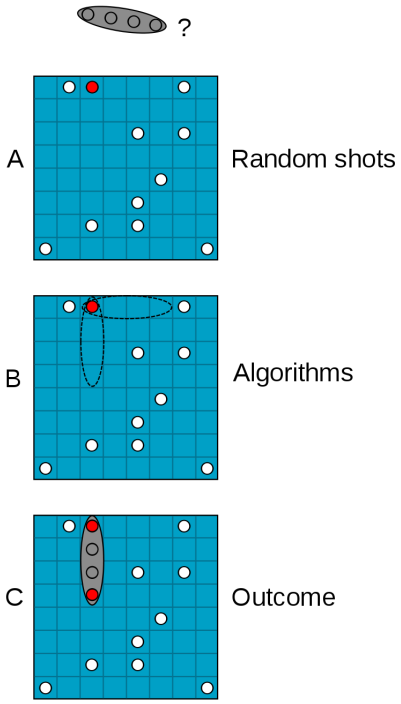
Overview

There is no single Monte Carlo method; instead, the term describes a large and widely-used class of approaches. However, these approaches tend to follow a particular pattern:

1. Define a domain of possible inputs.
2. Generate inputs randomly from the domain.
3. Perform a deterministic computation using the inputs.
4. Aggregate the results of the individual computations into the final result.

For example, the value of π can be approximated using a Monte Carlo method:

1. Draw a square on the ground, then inscribe a circle within it. From plane geometry, the ratio of the area of an inscribed circle to that of the surrounding square is π/4.
2. Uniformly scatter some objects of uniform size throughout the square. For example, grains of rice or sand.
3. Since the two areas are in the ratio π/4, the objects should fall in the areas in approximately the same ratio. Thus, counting the number of objects in the circle and dividing by the total number of objects in the square will yield an approximation for π/4. Multiplying the result by 4 will then yield an approximation for π itself.



The Monte Carlo method can be illustrated as a game of battleship. First a player makes some random shots. Next the player applies algorithms (i.e. a battleship is four dots in the vertical or horizontal direction). Finally based on the outcome of the random sampling and the algorithm the player can determine the likely locations of the other player's ships.

Notice how the π approximation follows the general pattern of Monte Carlo algorithms. First, we define a domain of inputs: in this case, it's the square which circumscribes our circle. Next, we generate inputs randomly (scatter individual grains within the square), then perform a computation on each input (test whether it falls within the circle). At the end, we aggregate the results into our final result, the approximation of π. Note, also, two other common properties of Monte Carlo methods: the computation's reliance on good random numbers, and its slow convergence to a better approximation as more data points are sampled. If grains are purposefully dropped into only, for example, the center of the circle, they will not be uniformly distributed, and so our approximation will be poor. An approximation will also be poor if only a few grains are randomly dropped into the whole square. Thus, the approximation of π will become more accurate both as the grains are dropped more uniformly and as more are dropped.

History

The name "Monte Carlo" was popularized by physics researchers Stanislaw Ulam, Enrico Fermi, John von Neumann, and Nicholas Metropolis, among others; the name is a reference to the Monte Carlo Casino in Monaco where Ulam's uncle would borrow money to gamble.[4] The use of randomness and the repetitive nature of the process are analogous to the activities conducted at a casino.

Random methods of computation and experimentation (generally considered forms of stochastic simulation) can be arguably traced back to the earliest pioneers of probability theory (see, e.g., Buffon's needle, and the work on small samples by William Sealy Gosset), but are more specifically traced to the pre-electronic computing era. The general difference usually described about a Monte Carlo form of simulation is that it systematically "inverts" the typical mode of simulation, treating deterministic problems by *first* finding a probabilistic analog (see Simulated annealing). Previous methods of simulation and statistical sampling generally did the opposite: using simulation to test a previously understood deterministic problem. Though examples of an "inverted" approach do exist historically, they were not considered a general method until the popularity of the Monte Carlo method spread.

Perhaps the most famous early use was by Enrico Fermi in 1930, when he used a random method to calculate the properties of the newly-discovered neutron. Monte Carlo methods were central to the simulations required for the Manhattan Project, though were severely limited by the computational tools at the time. Therefore, it was only after electronic computers were first built (from 1945 on) that Monte Carlo methods began to be studied in depth. In the 1950s they were used at Los Alamos for early work relating to the development of the hydrogen bomb, and became popularized in the fields of physics, physical chemistry, and operations research. The Rand Corporation and the U.S. Air Force were two of the major organizations responsible for funding and disseminating information on Monte Carlo methods during this time, and they began to find a wide application in many different fields.

Uses of Monte Carlo methods require large amounts of random numbers, and it was their use that spurred the development of pseudorandom number generators, which were far quicker to use than the tables of random numbers which had been previously used for statistical sampling.

Applications

As mentioned, Monte Carlo simulation methods are especially useful for modeling phenomena with significant uncertainty in inputs and in studying systems with a large number of coupled degrees of freedom. Specific areas of application include:

Physical sciences

Monte Carlo methods are very important in computational physics, physical chemistry, and related applied fields, and have diverse applications from complicated quantum chromodynamics calculations to designing heat shields and aerodynamic forms. The Monte Carlo method is widely used in → statistical physics, in particular, → Monte Carlo molecular modeling as an alternative for computational → molecular dynamics; see Monte Carlo method in statistical physics. In experimental particle physics, these methods are used for

designing detectors, understanding their behavior and comparing experimental data to theory.

Design and visuals

Monte Carlo methods have also proven efficient in solving coupled integral differential equations of radiation fields and energy transport, and thus these methods have been used in global illumination computations which produce photorealistic images of virtual 3D models, with applications in video games, architecture, design, computer generated films, special effects in cinema.

Finance and business

Monte Carlo methods in finance are often used to calculate the value of companies, to evaluate investments in projects at corporate level or to evaluate financial derivatives. The Monte Carlo method is intended for financial analysts who want to construct stochastic or probabilistic financial models as opposed to the traditional static and deterministic models. For its use in the insurance industry, see stochastic modelling.

Telecommunications

When planning a wireless network, design must be proved to work for a wide variety of scenarios that depend mainly on the number of users, their locations and the services they want to use. Monte Carlo methods are typically used to generate these users and their states. The network performance is then evaluated and, if results are not satisfactory, the network design goes through an optimization process.

Games

Monte Carlo methods have recently been applied in game playing related artificial intelligence theory. Most notably the game of Go has seen remarkably successful Monte Carlo algorithm based computer players. One of the main problems that this approach has in game playing is that it sometimes misses an isolated, very good move. These approaches are often strong strategically but weak tactically, as tactical decisions tend to rely on a small number of crucial moves which are easily missed by the randomly searching Monte Carlo algorithm.

Monte Carlo simulation versus “what if” scenarios

The opposite of Monte Carlo simulation might be considered deterministic modeling using single-point estimates. Each uncertain variable within a model is assigned a “best guess” estimate. Various combinations of each input variable are manually chosen (such as best case, worst case, and most likely case), and the results recorded for each so-called “what if” scenario. [5]

By contrast, Monte Carlo simulation considers random sampling of probability distribution functions as model inputs to produce hundreds or thousands of possible outcomes instead of a few discrete scenarios. The results provide probabilities of different outcomes occurring. [6] For example, a comparison of a spreadsheet cost construction model run using traditional “what if” scenarios, and then run again with Monte Carlo simulation and Triangular probability distributions shows that the Monte Carlo analysis has a narrower range than the “what if” analysis. This is because the “what if” analysis gives equal weight

to all scenarios.[7]

For an application, see quantifying uncertainty under corporate finance.

Use in mathematics

In general, Monte Carlo methods are used in mathematics to solve various problems by generating suitable random numbers and observing that fraction of the numbers obeying some property or properties. The method is useful for obtaining numerical solutions to problems which are too complicated to solve analytically. The most common application of the Monte Carlo method is Monte Carlo integration.

Integration

Deterministic methods of numerical integration operate by taking a number of evenly spaced samples from a function. In general, this works very well for functions of one variable. However, for functions of vectors, deterministic quadrature methods can be very inefficient. To numerically integrate a function of a two-dimensional vector, equally spaced grid points over a two-dimensional surface are required. For instance a 10x10 grid requires 100 points. If the vector has 100 dimensions, the same spacing on the grid would require 10^{100} points—far too many to be computed. 100 dimensions is by no means unreasonable, since in many physical problems, a "dimension" is equivalent to a degree of freedom. (See Curse of dimensionality.)

Monte Carlo methods provide a way out of this exponential time-increase. As long as the function in question is reasonably well-behaved, it can be estimated by randomly selecting points in 100-dimensional space, and taking some kind of average of the function values at these points. By the law of large numbers, this method will display $1/\sqrt{N}$ convergence—i.e. quadrupling the number of sampled points will halve the error, regardless of the number of dimensions.

A refinement of this method is to somehow make the points random, but more likely to come from regions of high contribution to the integral than from regions of low contribution. In other words, the points should be drawn from a distribution similar in form to the integrand. Understandably, doing this precisely is just as difficult as solving the integral in the first place, but there are approximate methods available: from simply making up an integrable function thought to be similar, to one of the adaptive routines discussed in the topics listed below.

A similar approach involves using low-discrepancy sequences instead—the → quasi-Monte Carlo method. Quasi-Monte Carlo methods can often be more efficient at numerical integration because the sequence "fills" the area better in a sense and samples more of the most important points that can make the simulation converge to the desired solution more quickly.

Integration methods

- Direct sampling methods
  - Importance sampling
  - Stratified sampling
  - Recursive stratified sampling
  - VEGAS algorithm
- Random walk Monte Carlo including Markov chains
  - Metropolis-Hastings algorithm
- Gibbs sampling

Optimization

Another powerful and very popular application for random numbers in numerical simulation is in numerical optimization. These problems use functions of some often large-dimensional vector that are to be minimized (or maximized). Many problems can be phrased in this way: for example a computer chess program could be seen as trying to find the optimal set of, say, 10 moves which produces the best evaluation function at the end. The traveling salesman problem is another optimization problem. There are also applications to engineering design, such as multidisciplinary design optimization.

Most Monte Carlo optimization methods are based on random walks. Essentially, the program will move around a marker in multi-dimensional space, tending to move in directions which lead to a lower function, but sometimes moving against the gradient.

Optimization methods

- Evolution strategy
- Genetic algorithms
- Parallel tempering
- Simulated annealing
- Stochastic optimization
- Stochastic tunneling

Inverse problems

Probabilistic formulation of inverse problems leads to the definition of a probability distribution in the model space. This probability distribution combines *a priori* information with new information obtained by measuring some observable parameters (data). As, in the general case, the theory linking data with model parameters is nonlinear, the a posteriori probability in the model space may not be easy to describe (it may be multimodal, some moments may not be defined, etc.).

When analyzing an inverse problem, obtaining a maximum likelihood model is usually not sufficient, as we normally also wish to have information on the resolution power of the data. In the general case we may have a large number of model parameters, and an inspection of the marginal probability densities of interest may be impractical, or even useless. But it is possible to pseudorandomly generate a large collection of models according to the posterior probability distribution and to analyze and display the models in such a way that information on the relative likelihoods of model properties is conveyed to the spectator. This can be accomplished by means of an efficient Monte Carlo method, even in cases where no explicit formula for the a priori distribution is available.

The best-known importance sampling method, the Metropolis algorithm, can be generalized, and this gives a method that allows analysis of (possibly highly nonlinear) inverse problems with complex a priori information and data with an arbitrary noise distribution. For details, see Mosegaard and Tarantola (1995),[8] or Tarantola (2005).[9]

Computational mathematics

Monte Carlo methods are useful in many areas of computational mathematics, where a *lucky choice* can find the correct result. A classic example is Rabin's algorithm for primality testing: for any n which is not prime, a random x has at least a 75% chance of proving that n is not prime. Hence, if n is not prime, but x says that it might be, we have observed at most a 1-in-4 event. If 10 different random x say that "n is probably prime" when it is not, we have observed a one-in-a-million event. In general a Monte Carlo algorithm of this kind produces one correct answer with a guarantee ***n* is composite, and *x* proves it so**, but another one without, but with a guarantee of not getting this answer when it is wrong **too often** — in this case at most 25% of the time. See also Las Vegas algorithm for a related, but different, idea.

Monte Carlo and random numbers

Interestingly, Monte Carlo simulation methods do not always require truly random numbers to be useful — while for some applications, such as primality testing, unpredictability is vital (see Davenport (1995)).[10] Many of the most useful techniques use deterministic, pseudo-random sequences, making it easy to test and re-run simulations. The only quality usually necessary to make good simulations is for the pseudo-random sequence to appear "random enough" in a certain sense.

What this means depends on the application, but typically they should pass a series of statistical tests. Testing that the numbers are uniformly distributed or follow another desired distribution when a large enough number of elements of the sequence are considered is one of the simplest, and most common ones.

See also

General

- Auxiliary field Monte Carlo
- Bootstrapping (statistics)
- Demon algorithm
- Evolutionary Computation
- Las Vegas algorithm
- Markov chain
- → Molecular dynamics
- Monte Carlo option model
- → Monte Carlo integration
- → Quasi-Monte Carlo method
- Random number generator
- Randomness
- Resampling (statistics)

Application areas

- Graphics, particularly for ray tracing; a version of the Metropolis-Hastings algorithm is also used for ray tracing where it is known as Metropolis light transport
- Modeling light transport in biological tissue
- Monte Carlo methods in finance
- Reliability engineering
- In simulated annealing for protein structure prediction
- In semiconductor device research, to model the transport of current carriers
- Environmental science, dealing with contaminant behavior
- Search And Rescue and Counter-Pollution. Models used to predict the drift of a life raft or movement of an oil slick at sea.
- In probabilistic design for simulating and understanding the effects of variability
- In physical chemistry, particularly for simulations involving atomic clusters
- In biomolecular simulations
- In polymer physics
  - Bond fluctuation model
- In computer science
  - Las Vegas algorithm
  - LURCH
  - Computer go
  - General Game Playing
- Modeling the movement of impurity atoms (or ions) in plasmas in existing and tokamaks (e.g.: DIVIMP).
- Nuclear and particle physics codes using the Monte Carlo method:
  - GEANT — CERN's simulation of high energy particles interacting with a detector.
  - CompHEP, PYTHIA — Monte-Carlo generators of particle collisions
  - MCNP(X) - LANL's radiation transport codes
  - MCU: universal computer code for simulation of particle transport (neutrons, photons, electrons) in three-dimensional systems by means of the Monte Carlo method
  - EGS — Stanford's simulation code for coupled transport of electrons and photons
  - PEREGRINE: LLNL's Monte Carlo tool for radiation therapy dose calculations
  - BEAMnrc — Monte Carlo code system for modeling radiotherapy sources (LINAC's)
  - PENELOPE — Monte Carlo for coupled transport of photons and electrons, with applications in radiotherapy
  - MONK — Serco Assurance's code for the calculation of k-effective of nuclear systems
- Modelling of foam and cellular structures
- Modeling of tissue morphogenesis
- Computation of holograms
- Phylogenetic analysis, i.e. Bayesian inference, Markov chain Monte Carlo

Other methods employing Monte Carlo

- Assorted random models, e.g. self-organised criticality
- Direct simulation Monte Carlo
- Dynamic Monte Carlo method
- Kinetic Monte Carlo
- → Quantum Monte Carlo
- → Quasi-Monte Carlo method using low-discrepancy sequences and self avoiding walks
- Semiconductor charge transport and the like
- Electron microscopy beam-sample interactions
- Stochastic optimization
- Cellular Potts model
- Markov chain Monte Carlo
- Cross-entropy method
- Applied information economics
- Monte Carlo localization

Notes

[1] Douglas Hubbard "How to Measure Anything: Finding the Value of Intangibles in Business" pg. 46, John Wiley & Sons, 2007

[2] Douglas Hubbard "The Failure of Risk Management: Why It's Broken and How to Fix It", John Wiley & Sons, 2009

[3] Nicholas Metropolis (1987), " The beginning of the Monte Carlo method (http://library.lanl.gov/la-pubs/00326866.pdf)", *Los Alamos Science* (1987 Special Issue dedicated to Stanislaw Ulam): 125–130,

[4] Douglas Hubbard "How to Measure Anything: Finding the Value of Intangibles in Business" pg. 46, John Wiley & Sons, 2007

[5] David Vose: “Risk Analysis, A Quantitative Guide,” Second Edition, p. 13, John Wiley & Sons, 2000.

[6] Ibid, p. 16

[7] Ibid, p. 17, showing graph

[8] http://www.ipgp.jussieu.fr/~tarantola/Files/Professional/Papers_PDF/MonteCarlo_latex.pdf

[9] http://www.ipgp.jussieu.fr/~tarantola/Files/Professional/SIAM/index.html

[10] Davenport, J. H.. "Primality testing revisited" (http://doi.acm.org/10.1145/143242.143290). doi: http://doi.acm.org/10.1145/143242.143290 (http://dx.doi.org/http://doi.acm.org/10.1145/143242.143290). . Retrieved on 2007-08-19.

References

- Metropolis, N.; Ulam, S. (1949). "The Monte Carlo Method". *Journal of the American Statistical Association* **44** (247): 335–341. doi: 10.2307/2280232 (http://dx.doi.org/10.2307/2280232).
- Metropolis, Nicholas; Rosenbluth, Arianna W.; Rosenbluth, Marshall N.; Teller, Augusta H.; Teller, Edward (1953). "Equation of State Calculations by Fast Computing Machines". *Journal of Chemical Physics* **21** (6): 1087. doi: 10.1063/1.1699114 (http://dx.doi.org/10.1063/1.1699114).
- Hammersley, J. M.; Handscomb, D. C. (1975). *Monte Carlo Methods*. London: Methuen. ISBN 0416523404.
- Kahneman, D.; Tversky, A. (1982). *Judgement under Uncertainty: Heuristics and Biases*. Cambridge University Press.
- Gould, Harvey; Tobochnik, Jan (1988). *An Introduction to Computer Simulation Methods, Part 2, Applications to Physical Systems*. Reading: Addison-Wesley. ISBN 020116504X.

- Binder, Kurt (1995). *The Monte Carlo Method in Condensed Matter Physics*. New York: Springer. ISBN 0387543694.
- Berg, Bernd A. (2004). *Markov Chain Monte Carlo Simulations and Their Statistical Analysis (With Web-Based Fortran Code)*. Hackensack, NJ: World Scientific. ISBN 9812389350.
- Caflisch, R. E. (1998). *Monte Carlo and quasi-Monte Carlo methods*. Acta Numerica. **7**. Cambridge University Press. pp. 1–49.
- Doucet, Arnaud; Freitas, Nando de; Gordon, Neil (2001). *Sequential Monte Carlo methods in practice*. New York: Springer. ISBN 0387951466.
- Fishman, G. S. (1995). *Monte Carlo: Concepts, Algorithms, and Applications*. New York: Springer. ISBN 038794527X.
- MacKeown, P. Kevin (1997). *Stochastic Simulation in Physics*. New York: Springer. ISBN 9813083263.
- Robert, C. P.; Casella, G. (2004). *Monte Carlo Statistical Methods* (2nd ed.). New York: Springer. ISBN 0387212396.
- Rubinstein, R. Y.; Kroese, D. P. (2007). *Simulation and the Monte Carlo Method* (2nd ed.). New York: John Wiley & Sons. ISBN 9780470177938.
- Mosegaard, Klaus; Tarantola, Albert (1995). "Monte Carlo sampling of solutions to inverse problems". *J. Geophys. Res.* **100** (B7): 12431–12447. doi: 10.1029/94JB03097 (http://dx.doi.org/10.1029/94JB03097).
- Tarantola, Albert (2005). *Inverse Problem Theory (http://www.ipgp.jussieu.fr/~tarantola/Files/Professional/SIAM/index.html)*. Philadelphia: Society for Industrial and Applied Mathematics. ISBN 0898715725. http://www.ipgp.jussieu.fr/~tarantola/Files/Professional/SIAM/index.html.

External links

- Overview and reference list (http://mathworld.wolfram.com/MonteCarloMethod.html), Mathworld
- Introduction to Monte Carlo Methods (http://www.ipp.mpg.de/de/for/bereiche/stellarator/Comp_sci/CompScience/csep/csep1.phy.ornl.gov/mc/mc.html), Computational Science Education Project
- Overview of formulas used in Monte Carlo simulation (http://www.sitmo.com/eqcat/15), the Quant Equation Archive, at sitmo.com
- The Basics of Monte Carlo Simulations (http://www.chem.unl.edu/zeng/joy/mclab/mcintro.html), University of Nebraska-Lincoln
- Introduction to Monte Carlo simulation (http://office.microsoft.com/en-us/assistance/HA011118931033.aspx) (for Excel), Wayne L. Winston
- Monte Carlo Methods - Overview and Concept (http://www.brighton-webs.co.uk/montecarlo/concept.asp), brighton-webs.co.uk
- Molecular Monte Carlo Intro (http://www.cooper.edu/engineering/chemechem/monte.html), Cooper Union
- Monte Carlo techniques applied in physics (http://homepages.ed.ac.uk/s0095122/Applet1-page.htm)
- MonteCarlo Simulation in Finance (http://www.global-derivatives.com/maths/k-o.php), global-derivatives.com
- Approximation of π with the Monte Carlo Method (http://twt.mpei.ac.ru/MAS/Worksheets/approxpi.mcd)

- Risk Analysis in Investment Appraisal (http://papers.ssrn.com/sol3/papers.cfm?abstract_id=265905), The Application of Monte Carlo Methodology in Project Appraisal, Savvakis C. Savvides
- Probabilistic Assessment of Structures using the Monte Carlo method (http://en.wikiversity.org/wiki/Probabilistic_Assessment_of_Structures), Wikiuniversity paper for students of Structural Engineering
- A very intuitive and comprehensive introduction to Quasi-Monte Carlo methods (http://www.puc-rio.br/marco.ind/quasi_mc.html)
- Pricing using Monte Carlo simulation (http://knol.google.com/k/giancarlo-vercellino/pricing-using-monte-carlo-simulation/11d5i2rgd9gn5/3#), a practical example, Prof. Giancarlo Vercellino

Software

- The BUGS project (http://www.mrc-bsu.cam.ac.uk/bugs/) (including WinBUGS and OpenBUGS)
- Monte Carlo Simulation, Resampling, Bootstrap tool (http://www.statistics101.net)
- YASAI: Yet Another Simulation Add-In (http://yasai.rutgers.edu/) - Free Monte Carlo Simulation Add-In for Excel created by Rutgers University

Monte Carlo molecular modeling

Monte Carlo molecular modeling is the application of → Monte Carlo methods to molecular problems. These problems can also be modeled by the → molecular dynamics method. The difference is that this approach relies on → statistical mechanics rather than molecular dynamics. Instead of trying to reproduce the dynamics of a system, it generates states according to appropriate Boltzmann probabilities. Thus, it is the application of the **Metropolis Monte Carlo simulation** to molecular systems. It is therefore also a particular subset of the more general Monte Carlo method in statistical physics.

It employs a Markov chain procedure in order to determine a **new state** for a system from a previous one. According to its stochastic nature, this new state is accepted at random. Each trial usually counts as a **move**. The avoidance of dynamics restricts the method to studies of static quantities only, but the freedom to choose moves makes the method very flexible. These moves must only satisfy a basic condition of **balance** in order equilibrium be properly described, but **detailed balance**, a stronger condition, is usually imposed when designing new algorithms. An additional advantage is that some systems, such as the Ising model, lack a dynamical description and are only defined by an energy prescription; for these the Monte Carlo approach is the only one feasible.

The great success of this method in statistical mechanics has led to various generalizations such as the method of simulated annealing for optimization, in which a fictitious temperature is introduced and then gradually lowered.

See also

- → Quantum Monte Carlo
- Monte Carlo method in statistical physics
- Software for molecular mechanics modeling
- Bond fluctuation model

External links

- http://cmm.cit.nih.gov/intro_simulation/node25.html
- http://members.aol.com/btluke/metro01.htm

References

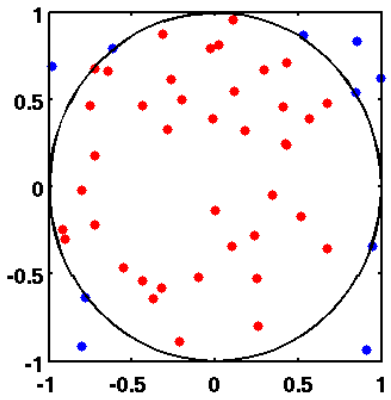
- Allen, M.P. and Tildesley, D.J. (1987). *Computer Simulation of Liquids*. Oxford University Press. ISBN 0-19-855645-4.
- Frenkel, D. and Smit, B. (2001). *Understanding Molecular Simulation*. Academic Press. ISBN 0-12-267351-4.
- Binder, K. and Heermann, D.W. (2002). *Monte Carlo Simulation in Statistical Physics. An Introduction (4th edition)*. Springer. ISBN 3-540-43221-3.

Monte Carlo integration

In mathematics, **Monte Carlo integration** is numerical integration using random numbers. That is, Monte Carlo integration methods are algorithms for the approximate evaluation of definite integrals, usually multidimensional ones. The usual algorithms evaluate the integrand at a regular grid. Monte Carlo methods, however, randomly choose the points at which the integrand is evaluated.

Informally, to estimate the area of a domain D, first pick a simple domain d whose area is easily calculated and which contains D. Now pick a sequence of random points that fall within d. Some fraction of these points will also fall within D. The area of D is then estimated as this fraction multiplied by the area of d.

The traditional Monte Carlo algorithm distributes the evaluation points uniformly over the integration region. Adaptive algorithms such as VEGAS and MISER use importance sampling and stratified sampling techniques to get a better result.



An illustration of Monte Carlo integration. In this example, the domain D is the inner circle and the domain d is the square. Because the square's area can be easily calculated, the area of the circle can be estimated by the ratio (0.8) of the points inside the circle (40) to the total number of points (50), yielding an approximation for $\pi/4 \approx 0.785$

Plain pseudo-random sampling

The algorithm computes an estimate of a multidimensional definite integral of the form,

$$I = \int_{a_1}^{b_1} dx_1 \int_{a_2}^{b_2} dx_2 \ldots \int_{a_n}^{b_n} dx_n \, f(x_1, x_2, \ldots, x_n) \equiv \int_V f(p)\, dV$$

where $p = \{x_1, \ldots, x_n\}$ and the hypercube V is the integration volume,

$$V = \{p | a_1 \leq x_1 \leq b_1, a_2 \leq x_2 \leq b_2, \ldots, a_n \leq x_n \leq b_n\} .$$

The plain Monte Carlo algorithm samples points uniformly from the integration region to estimate the integral and its error. Suppose that the sample has size *N* and denote the points in the sample by p_1, ..., p_N. Then the estimate for the integral is given by

$$I \approx Q \equiv V \frac{1}{N} \sum_{i=1}^{N} f(p_i) = V \langle f \rangle ,$$

where $\langle f \rangle$ denotes the sample mean of the integrand.

The variance of the function can be estimated using

$$\mathrm{var}(f) \equiv \sigma^2 = \frac{1}{N} \sum_{i=1}^{N} (f(p_i) - \langle f \rangle)^2.$$

According to the central limit theorem the variance of the estimate of the integral can be estimated as

$$\mathrm{var}(Q) = V^2 \frac{\mathrm{var}(f)}{N} = V^2 \frac{\sigma^2}{N}.$$

For large *N* this variance decreases asymptotically as $1/N$. The error estimate,

$$\delta Q \approx \sqrt{\mathrm{var}(Q)} = V \frac{\sigma}{\sqrt{N}},$$

decreases as $1/\sqrt{N}$. The familiar law of random walk applies: to reduce the error by a factor of 10 requires a 100-fold increase in the number of sample points.

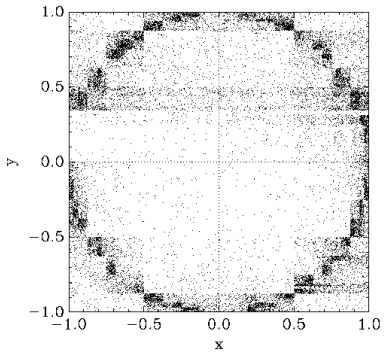
The above expression provides a statistical estimate of the error on the result. This error estimate is not a strict error bound — random sampling of the region may not uncover all the important features of the function, resulting in an underestimate of the error.

Recursive stratified sampling

Recursive stratified sampling is a generalization of one-dimensional adaptive quadratures to multi-dimensional integrals. On each recursion step the integral and the error are estimated using a plain Monte Carlo algorithm. If the error estimate is larger than the required accuracy the integration volume is divided into sub-volumes and the procedure is recursively applied to sub-volumes.

The ordinary `dividing by two' strategy does not work for multi-dimensions as the number of sub-volumes grows way too fast to keep track of. Instead one estimates along which dimension a subdivision should bring the most dividends and only subdivides the volume along this dimension.

Here is a typical algorithm for recursive stratified sampling:



An illustration of Recursive Stratified Sampling. In this example, the function $f(x,y) = (x^2 + y^2 < 1)?1 : 0$ from the above illustration was integrated within a unit square using the suggested algorithm. The sampled points were recorded and plotted. Clearly stratified sampling algorithm concentrates the points in the regions where the variation of the function is largest.

```
Sample N random points;
Estimate the average and the error;
If the error is acceptable :
   Return the average and the error;
Else :
   For each dimension :
      Subdivide the volume in two along the dimension;
      Estimate the sub-averages in the two sub-volumes;
   Pick the dimension with the largest sub-average;
   Subdivide the volume in two along this dimension;
   Dispatch two recursive calls to each of the sub-volumes;
   Estimate the grand average and grand variance;
   Return the grand average and grand variance;
```

The stratified sampling algorithm concentrates the sampling points in the regions where the variance of the function is largest thus reducing the grand variance and making the sampling more effective, as shown on the illustration.

The points for the illustration have been generated by the following JavaScript-1.8 implementation of the above algorithm,

```
function strata(f,a,b,acc,eps,N,aold,vold,nold,V)
{
if(typeof(N)=="undefined")N=42; // the number of points to be added at
each recursion
var randomx = function(a,b) [a[i]+Math.random()*(b[i]-a[i]) for (i in
a)]
var range   = function(n) {for(var i=0;i<n;i++) yield i}
var stats   = function(xs){ // statistics
  var xmean=xs.reduce(function(a,b)a+b,0)/xs.length
```

```
  var
sigma2=xs.reduce(function(a,b)a+b*b,0)/xs.length-Math.pow(xmean,2)
  return [xmean,Math.sqrt(sigma2),xs.length]
  }
if(typeof(aold)=="undefined"){ // first call: setting up 'old' values
  var V=1; for(let k in a) V*=(b[k]-a[k])
  let xs=[randomx(a,b) for(i in range(N))]
  let ys=[f(x) for each (x in xs)]
  var [aold,vold,nold]=stats(ys)
  }
var xs=[randomx(a,b) for(i in range(N))] // new points
var ys=[f(x) for each (x in xs)]         // new function values
var [av,va,]=stats(ys)                    // average and variance
var integ=V*(av*N+aold*nold)/(N+nold)    // integral and error
var error=V*Math.sqrt( (va*va*N+vold*vold*nold)/(N+nold)/(N+nold) )
if(error<acc+eps*Math.abs(integ)) return [integ,error]; // done
else{ // not done: need to dispatch a recursive call
  var vmax=-1, kmax=0
  for(let k in a){ // look in all dimensions for which is best to
bisect
     var [al,vl,nl]=stats([ys[i] for(i in xs)if(xs[i][k]<
(a[k]+b[k])/2)])
     var [ar,vr,nr]=stats([ys[i] for(i in
xs)if(xs[i][k]>=(a[k]+b[k])/2)])
     var v=Math.abs(al-ar) // take the one with largest variation
     if(v>vmax){ // remember the values
        vmax=v;kmax=k;
        var alo=al, vlo=vl, nlo=nl; var aro=ar, vro=vr, nro=nr
     }
  } // now dispatch two recursive calls
  let a2=a.slice(); a2[kmax]=(a[kmax]+b[kmax])/2
  let b2=b.slice(); b2[kmax]=(a[kmax]+b[kmax])/2
  let [i1,e1]=strata(f,a,b2,acc/1.414,eps,N,alo,vlo,nlo,V/2)
  let [i2,e2]=strata(f,a2,b,acc/1.414,eps,N,aro,vro,nro,V/2)
  return [i1+i2,Math.sqrt(e1*e1+e2*e2)] // return results
  }
}
var points=[]
var fun=function([x,y]){
   points.push([x,y])
   return x*x+y*y<1 ? 1:0
   }
var a=[-1,-1], b=[1,1]
var acc=eps=0.5e-2
var [q,err]=strata(fun,a,b,acc,eps,32)
print("# m=0, S=1")
for each(var [x,y] in points) print(x,y)
```

The popular MISER routine implements a similar algorithm.

MISER Monte Carlo

The MISER algorithm of Press and Farrar is based on recursive stratified sampling. This technique aims to reduce the overall integration error by concentrating integration points in the regions of highest variance.

The idea of stratified sampling begins with the observation that for two disjoint regions a and b with Monte Carlo estimates of the integral $E_a(f)$ and $E_b(f)$ and variances $\sigma_a^2(f)$ and $\sigma_b^2(f)$, the variance $Var(f)$ of the combined estimate $E(f) = (1/2)(E_a(f) + E_b(f))$ is given by,

$$\mathrm{Var}(f) = (\sigma_a^2(f)/4N_a) + (\sigma_b^2(f)/4N_b)$$

It can be shown that this variance is minimized by distributing the points such that,

$$N_a/(N_a + N_b) = \sigma_a/(\sigma_a + \sigma_b)$$

Hence the smallest error estimate is obtained by allocating sample points in proportion to the standard deviation of the function in each sub-region.

The MISER algorithm proceeds by bisecting the integration region along one coordinate axis to give two sub-regions at each step. The direction is chosen by examining all d possible bisections and selecting the one which will minimize the combined variance of the two sub-regions. The variance in the sub-regions is estimated by sampling with a fraction of the total number of points available to the current step. The same procedure is then repeated recursively for each of the two half-spaces from the best bisection. The remaining sample points are allocated to the sub-regions using the formula for N_a and N_b. This recursive allocation of integration points continues down to a user-specified depth where each sub-region is integrated using a plain Monte Carlo estimate. These individual values and their error estimates are then combined upwards to give an overall result and an estimate of its error.

This routines uses the MISER Monte Carlo algorithm to integrate the function f over the dim-dimensional hypercubic region defined by the lower and upper limits in the arrays xl and xu, each of size dim. The integration uses a fixed number of function calls, and obtains random sampling points using the random number generator r. A previously allocated workspace s must be supplied. The result of the integration is returned in result, with an estimated absolute error abserr.

Configurable Parameters

The MISER algorithm has several configurable parameters.

estimate_frac

This parameter specifies the fraction of the currently available number of function calls which are allocated to estimating the variance at each recursive step. In the GNU Scientific Library's (GSL) implementation, the default value is 0.1.

min_calls

This parameter specifies the minimum number of function calls required for each estimate of the variance. If the number of function calls allocated to the estimate using estimate_frac falls below min_calls then min_calls are used instead. This ensures that each estimate

maintains a reasonable level of accuracy. In the GNU Scientific Library's implementation, the default value of min_calls is 16 * dim.

min_calls_per_bisection

This parameter specifies the minimum number of function calls required to proceed with a bisection step. When a recursive step has fewer calls available than min_calls_per_bisection it performs a plain Monte Carlo estimate of the current sub-region and terminates its branch of the recursion. In the GNU Scientific Library's implementation, the default value of this parameter is 32 * min_calls.

alpha

This parameter controls how the estimated variances for the two sub-regions of a bisection are combined when allocating points. With recursive sampling the overall variance should scale better than 1/N, since the values from the sub-regions will be obtained using a procedure which explicitly minimizes their variance. To accommodate this behavior the MISER algorithm allows the total variance to depend on a scaling parameter \alpha,

$$\mathrm{Var}(f) = \frac{\sigma_a}{N_a^\alpha} + \frac{\sigma_b}{N_b^\alpha}$$

The authors of the original paper describing MISER recommend the value $\alpha = 2$ as a good choice, obtained from numerical experiments, and this is used as the default value in the GNU Scientific Library's implementation.

dither

This parameter introduces a random fractional variation of size dither into each bisection, which can be used to break the symmetry of integrands which are concentrated near the exact center of the hypercubic integration region. In the GNU Scientific Library's implementation, the default value of dither is zero, so no variation is introduced. If needed, a typical value of dither is around 0.1.

Importance sampling

VEGAS Monte Carlo

The VEGAS algorithm of G.P.Lepage is based on importance sampling. It samples points from the probability distribution described by the function $|f|$, so that the points are concentrated in the regions that make the largest contribution to the integral.

In general, if the Monte Carlo integral of f is sampled with points distributed according to a probability distribution described by the function g, we obtain an estimate $E_g(f;N)$,
$E_g(f;N) = E(f/g;N)$
with a corresponding variance,

$Var_g(f;N) = Var(f/g;N)$

If the probability distribution is chosen as $g = |f|/I(|f|)$ then it can be shown that the variance $V_g(f;N)$ vanishes, and the error in the estimate will be zero. In practice it is not possible to sample from the exact distribution g for an arbitrary function, so importance sampling algorithms aim to produce efficient approximations to the desired distribution.

The VEGAS algorithm approximates the exact distribution by making a number of passes over the integration region while histogramming the function f. Each histogram is used to define a sampling distribution for the next pass. Asymptotically this procedure converges to the desired distribution. In order to avoid the number of histogram bins growing like K^d the probability distribution is approximated by a separable function: $g(x_1, x_2, \ldots) = g_1(x_1)g_2(x_2)\ldots$ so that the number of bins required is only Kd. This is equivalent to locating the peaks of the function from the projections of the integrand onto the coordinate axes. The efficiency of VEGAS depends on the validity of this assumption. It is most efficient when the peaks of the integrand are well-localized. If an integrand can be rewritten in a form which is approximately separable this will increase the efficiency of integration with VEGAS.

VEGAS incorporates a number of additional features, and combines both stratified sampling and importance sampling. The integration region is divided into a number of "boxes", with each box getting a fixed number of points (the goal is 2). Each box can then have a fractional number of bins, but if bins/box is less than two, Vegas switches to a kind variance reduction (rather than importance sampling).

This routines uses the VEGAS Monte Carlo algorithm to integrate the function f over the dim-dimensional hypercubic region defined by the lower and upper limits in the arrays xl and xu, each of size dim. The integration uses a fixed number of function calls calls, and obtains random sampling points using the random number generator r. A previously allocated workspace s must be supplied. The result of the integration is returned in $result$, with an estimated absolute error $abserr$. The result and its error estimate are based on a weighted average of independent samples. The chi-squared per degree of freedom for the weighted average is returned via the state struct component, $s \to chisq$, and must be consistent with 1 for the weighted average to be reliable.
The VEGAS algorithm computes a number of independent estimates of the integral internally, according to the iterations parameter described below, and returns their weighted average. Random sampling of the integrand can occasionally produce an estimate where the error is zero, particularly if the function is constant in some regions. An estimate with zero error causes the weighted average to break down and must be handled separately. In the original Fortran implementations of VEGAS the error estimate is made non-zero by substituting a small value (typically 1e-30). The implementation in GSL differs from this and avoids the use of an arbitrary constant -- it either assigns the value a weight which is the average weight of the preceding estimates, or discards it according to the following procedure:

- **Current estimate has zero error, weighted average has finite error**
  The current estimate is assigned a weight which is the average weight of the preceding estimates.
- **Current estimate has finite error, previous estimates had zero error**
  The previous estimates are discarded and the weighted averaging procedure begins with the current estimate.
- **Current estimate has zero error, previous estimates had zero error**
  The estimates are averaged using the arithmetic mean, but no error is computed.

Configurable Parameters

The VEGAS algorithm is configurable.

chisq

This parameter gives the chi-squared per degree of freedom for the weighted estimate of the integral. The value of chisq should be close to 1. A value of chisq which differs significantly from 1 indicates that the values from different iterations are inconsistent. In this case the weighted error will be under-estimated, and further iterations of the algorithm are needed to obtain reliable results.

alpha

The parameter alpha controls the stiffness of the rebinning algorithm. It is typically set between one and two. A value of zero prevents rebinning of the grid. In the GNU Scientific Library's implementation, the default value is 1.5.

iterations

The number of iterations to perform for each call to the routine. In the GNU Scientific Library's implementation, the default value is 5 iterations.

stage

Setting this determines the stage of the calculation. Normally, stage = 0 which begins with a new uniform grid and empty weighted average. Calling vegas with stage = 1 retains the grid from the previous run but discards the weighted average, so that one can "tune" the grid using a relatively small number of points and then do a large run with stage = 1 on the optimized grid. Setting stage = 2 keeps the grid and the weighted average from the previous run, but may increase (or decrease) the number of histogram bins in the grid depending on the number of calls available. Choosing stage = 3 enters at the main loop, so that nothing is changed, and is equivalent to performing additional iterations in a previous call.

mode

The possible choices are GSL_VEGAS_MODE_IMPORTANCE, GSL_VEGAS_MODE_STRATIFIED, GSL_VEGAS_MODE_IMPORTANCE_ONLY. This determines whether VEGAS will use importance sampling or stratified sampling, or whether it can pick on its own. In low dimensions VEGAS uses strict stratified sampling (more precisely, stratified sampling is chosen if there are fewer than 2 bins per box).

See also

- Auxiliary field Monte Carlo
- → Monte Carlo method

References and further reading

The following reference about Monte Carlo and quasi-Monte Carlo methods in general (with a description of the variance reduction techniques) is excellent to start with:

- R. E. Caflisch, *Monte Carlo and quasi-Monte Carlo methods*, Acta Numerica vol. 7, Cambridge University Press, 1998, pp. 1-49.

Nice survey on arXiv, based on lecture for graduate students in high energy physics:

- S. Weinzierl, *Introduction to Monte Carlo methods* [1],

The MISER algorithm is described in the following article,

- W.H. Press, G.R. Farrar, Recursive Stratified Sampling for Multidimensional Monte Carlo Integration, Computers in Physics, v4 (1990), pp190-195.

The VEGAS algorithm is described in the following papers,

- G.P. Lepage, A New Algorithm for Adaptive Multidimensional Integration, Journal of Computational Physics 27, 192-203, (1978)
- G.P. Lepage, VEGAS: An Adaptive Multi-dimensional Integration Program, Cornell preprint CLNS 80-447, March 1980

Early works:

- J. M. Hammersley, D.C. Handscomb (1964) Monte Carlo Methods. Methuen. ISBN 0-416-52340-4

Based on the GNU Scientific Library's manual, which is published under the GFDL (and hence free to use for Wikipedia). Original available here [2].

External links

- Module for Monte Carlo Integration [3]
- Internet Resources for Monte Carlo Integration [4]

References

[1] http://arxiv.org/abs/hep-ph/0006269/
[2] http://www.gnu.org/software/gsl/manual/gsl-ref_23.html
[3] http://math.fullerton.edu/mathews/n2003/MonteCarloMod.html
[4] http://math.fullerton.edu/mathews/n2003/montecarlo/MonteCarloBib/Links/MonteCarloBib_lnk_1.html

Quasi-Monte Carlo method

In numerical analysis, a **quasi-Monte Carlo method** is a method for the computation of an integral (or some other problem) that is based on low-discrepancy sequences. This is in contrast to a regular → Monte Carlo method, which is based on sequences of pseudorandom numbers.

Monte Carlo and quasi-Monte Carlo methods are stated in a similar way. The problem is to approximate the integral of a function f as the average of the function evaluated at a set of points x_1, ..., x_N.

$$\int_{\bar{I}^s} f(u)\,du \approx \frac{1}{N}\sum_{i=1}^{N} f(x_i),$$

where $\bar{I}^s$ is the s-dimensional unit cube, $\bar{I}^s = [0, 1] \times \ldots \times [0, 1]$. (Thus each x_i is a vector of s elements.) In a Monte Carlo method, the set x_1, ..., x_N is a subsequence of pseudorandom numbers. In a quasi-Monte Carlo method, the set is a subsequence of a low-discrepancy sequence.

The approximation error of a method of the above type is bounded by a term proportional to the discrepancy of the set x_1, ..., x_N, by the Koksma-Hlawka inequality. The discrepancy of sequences typically used for the quasi-Monte Carlo method is bounded by a constant times

$$\frac{(\log N)^s}{N}.$$

In comparison, with probability one, the expected discrepancy of a uniform random sequence (as used in the Monte Carlo method) has an order of convergence

$$\sqrt{\frac{\log\log N}{2N}}$$

by the law of the iterated logarithm.

Thus it would appear that the accuracy of the quasi-Monte Carlo method increases faster than that of the Monte Carlo method. However, Morokoff and Caflisch cite examples of problems in which the advantage of the quasi-Monte Carlo is less than expected theoretically. Still, in the examples studied by Morokoff and Caflisch, the quasi-Monte Carlo method did yield a more accurate result than the Monte Carlo method with the same number of points.

Morokoff and Caflisch remark that the advantage of the quasi-Monte Carlo method is greater if the integrand is smooth, and the number of dimensions s of the integral is small. A technique, coined randomized quasi-Monte Carlo, that mixes quasi-Monte Carlo with traditional Monte Carlo, extends the benefits of quasi-Monte Carlo to medium to large s.

Application areas

- Monte Carlo methods in finance

See also

- → Monte Carlo method

References

- Michael Drmota and Robert F. Tichy, *Sequences, discrepancies and applications*, Lecture Notes in Math., **1651**, Springer, Berlin, 1997, ISBN 3-540-62606-9
- Harald Niederreiter. *Random Number Generation and Quasi-Monte Carlo Methods.* Society for Industrial and Applied Mathematics, 1992. ISBN 0-89871-295-5
- Harald G. Niederreiter, *Quasi-Monte Carlo methods and pseudo-random numbers*, Bull. Amer. Math. Soc. **84** (1978), no. 6, 957--1041
- William J. Morokoff and Russel E. Caflisch, *Quasi-random sequences and their discrepancies*, SIAM J. Sci. Comput. **15** (1994), no. 6, 1251--1279 *(At CiteSeer:[1])*
- William J. Morokoff and Russel E. Caflisch, *Quasi-Monte Carlo integration*, J. Comput. Phys. **122** (1995), no. 2, 218--230. *(At CiteSeer: [2])*
- Oto Strauch and Štefan Porubský, *Distribution of Sequences: A Sampler*, Peter Lang Publishing House, Frankfurt am Main 2005, ISBN 3-631-54013-2
- R. E. Caflisch, *Monte Carlo and quasi-Monte Carlo methods*, Acta Numerica vol. 7, Cambridge University Press, 1998, pp. 1-49.

External links

- A very intuitive and comprehensive introduction to Quasi-Monte Carlo methods [3]

References

[1] http://citeseer.ist.psu.edu/morokoff94quasirandom.html
[2] http://citeseer.ist.psu.edu/morokoff95quasimonte.html
[3] http://www.puc-rio.br/marco.ind/quasi_mc.html

Quantum Dynamics

Quantum thermodynamics

In the physical sciences, **quantum thermodynamics** is the study of heat and work dynamics in quantum systems. Approximately, quantum thermodynamics attempts to combine thermodynamics and quantum mechanics into a coherent whole. The essential point at which "quantum mechanics" began was when, in 1900, Max Planck outlined the "quantum hypothesis", i.e. that the energy of atomic systems can be quantized, as based on the first two laws of thermodynamics as described by Rudolf Clausius (1865) and Ludwig Boltzmann (1877).[1] [2] See the history of quantum mechanics for a more detailed outline.

Overview

A central objective in quantum thermodynamics is the quantitative and qualitative determination of the laws of thermodynamics at the quantum level in which uncertainty and probability begin to take effect. A fundamental question is: what remains of thermodynamics if one goes to the extreme limit of small quantum systems having a few degrees of freedom? If thermodynamics applies at this level, are the many formulations of the second law of thermodynamics, i.e. the entropy of a closed system cannot decrease, heat flows from high to low temperature, systems evolve towards minimum potential energy wells, energy tends to dissipate, etc., still applicable, or is there a more “universal” formulation?

See also

- Quantum decoherence

References

[1] Planck, Max. (1900). *“ Entropy and Temperature of Radiant Heat (http://www.iee.org/publish/inspec/prodcat/1900A01446.xml).”* Annalen der Physick, vol. 1. no 4. April, pg. 719-37.

[2] Planck, Max. (1901). " *On the Law of Distribution of Energy in the Normal Spectrum (http://dbhs.wvusd.k12.ca.us/webdocs/Chem-History/Planck-1901/Planck-1901.html)*". Annalen der Physik, vol. 4, p. 553 ff.

Further reading

1. Gemmer, J., Michel, M., Mahler, G. (2005). *Quantum Thermodynamics – Emergence of Thermodynamic Behavior Within Composite Quantum Systems*. Springer. ISBN 3-540-22911-6.
2. Rudakov, E.S. (1998). *Molecular, Quantum and Evolution Thermodynamics: Development and Specialization of the Gibbs Method*.. Donetsk State University Press. ISBN 966-02-0708-5.

External links

- Quantum Thermodynamics and the Gibbs Paradox (http://staff.science.uva.nl/~nieuwenh/QL2L.html)
- Quantum Thermodynamics (http://www.chaos.org.uk/~eddy/physics/heat.html)
- On the Classical Limit of Quantum Thermodynamics in Finite Time (http://www.fh.huji.ac.il/~ronnie/Papers/geva92.pdf) [PDF-format]
- Quantum Thermodynamics (http://www.quantumthermodynamics.org) - list of good related articles

Quantum chemistry

Quantum chemistry is a branch of theoretical chemistry, which applies quantum mechanics and quantum field theory to address issues and problems in chemistry. The description of the electronic behavior of atoms and molecules as pertaining to their reactivity is one of the applications of quantum chemistry. Quantum chemistry lies on the border between chemistry and physics, and significant contributions have been made by scientists from both fields. It has a strong and active overlap with the field of atomic physics and molecular physics, as well as physical chemistry.

Quantum chemistry mathematically describes the fundamental behavior of matter at the molecular scale.[1] It is, in principle, possible to describe all chemical systems using this theory. In practice, only the simplest chemical systems may realistically be investigated in purely quantum mechanical terms, and approximations must be made for most practical purposes (e.g., Hartree-Fock, post Hartree-Fock or Density functional theory, see computational chemistry for more details). Hence a detailed understanding of quantum mechanics is not necessary for most chemistry, as the important implications of the theory (principally the orbital approximation) can be understood and applied in simpler terms.

In quantum mechanics the Hamiltonian, or the physical state, of a particle can be expressed as the sum of two operators, one corresponding to kinetic energy and the other to potential energy. The Hamiltonian in the Schrödinger wave equation used in quantum chemistry does not contain terms for the spin of the electron.

Solutions of the Schrödinger equation for the hydrogen atom gives the form of the wave function for atomic orbitals, and the relative energy of the various orbitals. The orbital approximation can be used to understand the other atoms e.g. helium, lithium and carbon.

History

The **history of quantum chemistry** essentially began with the 1838 discovery of cathode rays by Michael Faraday, the 1859 statement of the black body radiation problem by Gustav Kirchhoff, the 1877 suggestion by Ludwig Boltzmann that the energy states of a physical system could be discrete, and the 1900 quantum hypothesis by Max Planck that any energy radiating atomic system can theoretically be divided into a number of discrete energy elements ε such that each of these energy elements is proportional to the frequency ν with which they each individually radiate energy, as defined by the following formula:

$$\epsilon = h\nu$$

where h is a numerical value called Planck's Constant. Then, in 1905, to explain the photoelectric effect (1839), i.e., that shining light on certain materials can function to eject electrons from the material, Albert Einstein postulated, based on Planck's quantum hypothesis, that light itself consists of individual quantum particles, which later came to be called photons (1926). In the years to follow, this theoretical basis slowly began to be applied to chemical structure, reactivity, and bonding.

Electronic structure

The first step in solving a quantum chemical problem is usually solving the Schrödinger equation (or Dirac equation in relativistic quantum chemistry) with the electronic molecular Hamiltonian. This is called determining the **electronic structure** of the molecule. It can be said that the electronic structure of a molecule or crystal implies essentially its chemical properties.

Wave model

The foundation of quantum mechanics and quantum chemistry is the **wave model**, in which the atom is a small, dense, positively charged nucleus surrounded by electrons. Unlike the earlier Bohr model of the atom, however, the wave model describes electrons as "clouds" moving in orbitals, and their positions are represented by probability distributions rather than discrete points. The strength of this model lies in its predictive power. Specifically, it predicts the pattern of chemically similar elements found in the periodic table. The wave model is so named because electrons exhibit properties (such as interference) traditionally associated with waves. See wave-particle duality.

Valence bond

Although the mathematical basis of quantum chemistry had been laid by Schrödinger in 1926, it is generally accepted that the first true calculation in quantum chemistry was that of the German physicists Walter Heitler and Fritz London on the hydrogen (H_2) molecule in 1927. Heitler and London's method was extended by the American theoretical physicist John C. Slater and the American theoretical chemist Linus Pauling to become the **Valence-Bond (VB)** [or **Heitler-London-Slater-Pauling (HLSP)**] method. In this method, attention is primarily devoted to the pairwise interactions between atoms, and this method therefore correlates closely with classical chemists' drawings of bonds.

Molecular orbital

An alternative approach was developed in 1929 by Friedrich Hund and Robert S. Mulliken, in which electrons are described by mathematical functions delocalized over an entire molecule. The **Hund-Mulliken** approach or **molecular orbital (MO) method** is less intuitive to chemists, but has turned out capable of predicting spectroscopic properties better than the VB method. This approach is the conceptional basis of the **Hartree-Fock method** and further post Hartree-Fock methods.

Density functional theory

The **Thomas-Fermi model** was developed independently by Thomas and Fermi in 1927. This was the first attempt to describe many-electron systems on the basis of electronic density instead of wave functions, although it was not very successful in the treatment of entire molecules. The method did provide the basis for what is now known as **density functional theory**. Though this method is less developed than post Hartree-Fock methods, its lower computational requirements allow it to tackle larger polyatomic molecules and even macromolecules, which has made it the most used method in computational chemistry at present.

Chemical dynamics

A further step can consist of solving the Schrödinger equation with the total molecular Hamiltonian in order to study the motion of molecules. Direct solution of the Schrödinger equation is called *quantum molecular dynamics*, within the semiclassical approximation *semiclassical molecular dynamics*, and within the classical mechanics framework → *molecular dynamics (MD)*. Statistical approaches, using for example → Monte Carlo methods, are also possible.

Adiabatic chemical dynamics

Main article: Adiabatic formalism or Born-Oppenheimer approximation

In **adiabatic dynamics**, interatomic interactions are represented by single scalar potentials called potential energy surfaces. This is the Born-Oppenheimer approximation introduced by Born and Oppenheimer in 1927. Pioneering applications of this in chemistry were performed by Rice and Ramsperger in 1927 and Kassel in 1928, and generalized into the RRKM theory in 1952 by Marcus who took the transition state theory developed by Eyring in 1935 into account. These methods enable simple estimates of unimolecular reaction rates from a few characteristics of the potential surface.

Non-adiabatic chemical dynamics

Non-adiabatic dynamics consists of taking the interaction between several coupled potential energy surface (corresponding to different electronic quantum states of the molecule). The coupling terms are called **vibronic couplings**. The pioneering work in this field was done by Stueckelberg, Landau, and Zener in the 1930s, in their work on what is now known as the Landau-Zener transition. Their formula allows the transition probability between two diabatic potential curves in the neighborhood of an avoided crossing to be calculated.

Quantum chemistry and quantum field theory

The application of quantum field theory (QFT) to chemical systems and theories has become increasingly common in the modern physical sciences. One of the first and most fundamentally explicit appearances of this is seen in the theory of the photomagneton. In this system, plasmas, which are ubiquitous in both physics and chemistry, are studied in order to determine the basic quantization of the underlying bosonic field. However, quantum field theory is of interest in many fields of chemistry, including: nuclear chemistry, astrochemistry, sonochemistry, and quantum hydrodynamics. Field theoretic methods have

also been critical in developing the ab initio Effective Hamiltonian theory of semi-empirical pi-electron methods.

See also

- Atomic physics
- Computational chemistry
- Condensed matter physics
- International Academy of Quantum Molecular Science
- Physical chemistry
- Quantum chemistry computer programs
- Quantum electrochemistry
- QMC@Home
- Theoretical physics

Further reading

- Pauling, L. (1954). *General Chemistry*. Dover Publications. ISBN 0-486-65622-5.
- Pauling, L., and Wilson, E. B. *Introduction to Quantum Mechanics with Applications to Chemistry* (Dover Publications) ISBN 0-486-64871-0
- Atkins, P.W. *Physical Chemistry* (Oxford University Press) ISBN 0-19-879285-9
- McWeeny, R. *Coulson's Valence* (Oxford Science Publications) ISBN 0-19-855144-4
- Landau, L.D. and Lifshitz, E.M. *Quantum Mechanics:Non-relativistic Theory* (Course of Theoretical Physics vol.3) (Pergamon Press)
- Bernard Pullman and Alberte Pullman. 1963. *Quantum Biochemistry.*, New York and London: Academic Press.
- Eric R. Scerri, The Periodic Table: Its Story and Its Significance, Oxford University Press, 2006. Considers the extent to which chemistry and especially the periodic system has been reduced to quantum mechanics. ISBN 0-19-530573-6.
- Simon, Z. 1976. *Quantum Biochemistry and Specific Interactions.*, Taylor & Francis; ISBN-13: 978-0856260872 and ISBN 0-85-6260878 .

References

[1] "Quantum Chemistry" (http://cmm.cit.nih.gov/modeling/guide_documents/quantum_mechanics_document.html). *The NIH Guide to Molecular Modeling*. National Institutes of Health. . Retrieved on 2007-09-08.

External links

- The Sherrill Group - Notes (http://vergil.chemistry.gatech.edu/notes/index.html)
- ChemViz Curriculum Support Resources (http://www.shodor.org/chemviz/)
- Early ideas in the history of quantum chemistry (http://www.quantum-chemistry-history.com/)

Nobel lectures by quantum chemists

- Walter Kohn's Nobel lecture (http://nobelprize.org/chemistry/laureates/1998/kohn-lecture.html)
- Rudolph Marcus' Nobel lecture (http://nobelprize.org/chemistry/laureates/1992/marcus-lecture.html)
- Robert Mulliken's Nobel lecture (http://nobelprize.org/chemistry/laureates/1966/mulliken-lecture.html)
- Linus Pauling's Nobel lecture (http://nobelprize.org/chemistry/laureates/1954/pauling-lecture.html)
- John Pople's Nobel lecture (http://nobelprize.org/chemistry/laureates/1998/pople-lecture.html)

Quantum Monte Carlo

Electronic structure methods
Tight binding
Nearly-free electron model
Hartree–Fock
Modern valence bond
Generalized valence bond
Møller–Plesset perturbation theory
Configuration interaction
Coupled cluster
Multi-configurational self-consistent field
Density functional theory
Quantum chemistry composite methods
→ Quantum Monte Carlo
k·p perturbation theory
Muffin-tin approximation
LCAO method

Quantum Monte Carlo is a large class of computer algorithms that simulate quantum systems with the idea of solving the many-body problem. They use, in one way or another, the → Monte Carlo method to handle the many-dimensional integrals that arise. Quantum Monte Carlo allows a direct representation of many-body effects in the wavefunction, at the cost of statistical uncertainty that can be reduced with more simulation time. For bosons, there exist numerically exact and polynomial-scaling algorithms. For fermions, there exist very good approximations and numerically exact exponentially scaling quantum Monte Carlo algorithms, but none that are both.

Background

In principle, any physical system can be described by the many-body Schrödinger equation as long as the constituent particles are not moving "too" fast; that is, they are not moving near the speed of light. This includes the electrons in almost every material in the world, so if we could solve the Schrödinger equation, we could predict the behavior of any electronic system, which has important applications in fields from computers to biology. This also includes the nuclei in Bose–Einstein condensate and superfluids such as liquid helium. The difficulty is that the Schrödinger equation involves a function of three times the number of particles and is difficult to solve even using parallel computing technology in a reasonable amount of time (less than 2 years). Traditionally, theorists have approximated the many-body wave function as an antisymmetric function of one-body orbitals, as shown concisely at this link.[1] This kind of formulation either limits the possible wave functions, as in the case of the Hartree-Fock (HF) approximation, or converges very slowly, as in configuration interaction. One of the reasons for the difficulty with an HF initial estimate (ground state seed, also known as Slater determinant) is that it is very difficult to model the electronic and nuclear cusps in the wavefunction. However, one does not generally model at this point of the approximation. As two particles approach each other, the wavefunction has exactly known derivatives.

Quantum Monte Carlo is a way around these problems because it allows us to model a many-body wavefunction of our choice directly. Specifically, we can use a Hartree-Fock approximation as our starting point but then multiplying it by any symmetric function, of which Jastrow functions are typical, designed to enforce the cusp conditions. Most methods aim at computing the ground-state wavefunction of the system, with the exception of path integral Monte Carlo and finite-temperature auxiliary field Monte Carlo, which calculate the density matrix.

There are several quantum Monte Carlo methods, each of which uses Monte Carlo in different ways to solve the many-body problem:

Quantum Monte Carlo methods

- Variational Monte Carlo : A good place to start; it is commonly used in many sorts of quantum problems.
- Diffusion Monte Carlo : The most common high-accuracy method for electrons (that is, chemical problems), since it comes quite close to the exact ground-state energy fairly efficiently. Also used for simulating the quantum behavior of atoms, etc.
- Path integral Monte Carlo : Finite-temperature technique mostly applied to bosons where temperature is very important, especially superfluid helium.
- Auxiliary field Monte Carlo : Usually applied to lattice problems, although there has been recent work on applying it to electrons in chemical systems.
- Reptation Monte Carlo : Recent zero-temperature method related to path integral Monte Carlo, with applications similar to diffusion Monte Carlo but with some different tradeoffs.
- Gaussian quantum Monte Carlo

See also

- → Monte Carlo method
- QMC@Home
- → Quantum chemistry
- Density matrix renormalization group
- Time-evolving block decimation
- Metropolis algorithm
- Wavefunction optimization

References

[1] http://www.attaccalite.altervista.org/PhDThesis/html/node9.html

- Hammond, B.J.; W.A. Lester & P.J. Reynolds (1994) (in English). *Monte Carlo Methods in Ab Initio Quantum Chemistry (http://www.worldscibooks.com/chemistry/1170.html)*. Singapore: World Scientific. ISBN 981-02-0321-7. OCLC 29594695 (http://worldcat.org/oclc/29594695). http://www.worldscibooks.com/chemistry/1170.html. Retrieved on 2007-01-18.
- Nightingale, M.P.; Umrigar, Cyrus J., ed (1999) (in English). *Quantum Monte Carlo Methods in Physics and Chemistry (http://www.springer.com/west/0-7923-5552-0)*. Springer. ISBN 978-0-7923-5552-6. http://www.springer.com/west/0-7923-5552-0. Retrieved on 2007-01-18.
- W. M. C. Foulkes; L. Mitáš, R. J. Needs and G. Rajagopal (5 January 2001). " Quantum Monte Carlo simulations of solids (http://link.aps.org/abstract/RMP/v73/p33)" (in English) (abstract). *Rev. Mod. Phys.* **73**: 33–83. doi: 10.1103/RevModPhys.73.33 (http://dx.doi.org/10.1103/RevModPhys.73.33). http://link.aps.org/abstract/RMP/v73/p33. Retrieved on 2007-01-18.
- Raimundo R. dos Santos (2003). " Introduction to Quantum Monte Carlo simulations for fermionic systems (http://arxiv.org/abs/cond-mat/0303551v1)" (in English) (fulltext). *Braz. J. Phys.* **33**: 36. http://arxiv.org/abs/cond-mat/0303551v1. Retrieved on 2007-01-18.

External links

- QMCWIKI (http://www.qmcwiki.org/)
- Joint DEMOCRITOS-ICTP School on Continuum Quantum Monte Carlo Methods (http://cdsagenda5.ictp.trieste.it/full_display.php?ida=a0332&fid=)
- FreeScience Library -> Quantum Monte Carlo (http://freescience.info/books.php?id=35)
- UIUC 2007 Summer School on Computational Materials Science: Quantum Monte Carlo from Minerals and Materials to Molecules (http://www.mcc.uiuc.edu/summerschool/2007/qmc/)
- Quantum Monte Carlo in the Apuan Alps V (http://www.vallico.net/tti/tti.html) - international workshop, Vallico Sotto, Tuscany, 25 July-1 August 2009 (Click PUBLIC EVENTS) - Announcement (http://www.vallico.net/tti/qmcitaa_09/announcement.html), Poster (http://www.tcm.phy.cam.ac.uk/~mdt26/tti2/poster/tti_c_poster_2009.png)
- Quantum Monte Carlo and the CASINO program IV (http://www.vallico.net/tti/tti.html) - summer school, Vallico Sotto, Tuscany, 2-9 August 2009 (Click PUBLIC EVENTS) -

Announcement (http://www.vallico.net/tti/qmcatcp_09/announcement.html), Poster (http://www.tcm.phy.cam.ac.uk/~mdt26/tti2/poster/tti_ss_poster_2009.png)

Force field

A **force field**, sometimes known as an **energy shield**, **force shield**, or **deflector shield** is a barrier, typically made of energy or charged particles, that protects a person, area or object from attacks or intrusions. Force fields tend to appear often in works of speculative fiction.

In real life

A University of Washington in Seattle group has been experimenting with using a bubble of charged plasma to surround a spacecraft, contained by a fine mesh of superconducting wire.[1] This would protect the spacecraft from interstellar radiation and some particles without needing physical shielding.

Likewise, Rutherford Appleton Laboratory is attempting to design an actual test satellite, which should orbit Earth with a charged plasma field around it.[2] [3]

Workers at a 3M factory in South Carolina have encountered electrostatically-charged air that impeded movement, with the problem fixed by properly grounding the equipment causing the stray charges.[4]

Plasma windows have some similarities to force fields, being difficult for matter to transverse.

In fiction

Science fiction and fantasy venues postulate a number of potential uses for force fields:

- A barrier to allow workers to work in areas that can be exposed to the vacuum of space, keeping the atmosphere inside while allowing certain other objects to pass through.
- Emergency quarantine of an area afflicted by a harmful biological or chemical agent or occupied by enemy forces.
- The extinguishing of a fire by forcing the reaction to use up all the available oxygen in the confined space.
- As a shield (in some cases large enough to cover an entire planet) to protect something from damage by natural forces or enemy attack.
- To create a temporary habitable space in a place not usually suited to sustaining life.
- As a security method to direct someone in a particular direction for capture, or to confine a captive in a particular area.

The concept goes back at least as far as the 1920s, in the works of E.E. 'Doc' Smith and others; and William Hope Hodgson's *The Night Land* (1912) has the Last Redoubt, in which the remnants of humanity shelter, protected by something very like a force field.

The abilities and exact functionality of energy shields vary; in some works (such as in the Star Trek universe), energy shields can stop both energy and particle weapons (e.g. phasers) and normal projectiles, both natural and artificial; in others, such as the Star Wars universe, there are multiple types of force fields that defend against different sorts of

attacks.

Energy shields usually work by absorbing or dissipating the energy of the incoming attack; prolonged exposure to such attacks weakens the shield and eventually results in the shield's collapse, making the ship's hull (or building's walls, or planet's surface) vulnerable to attack. An example of this is the aerial Scrin Battleships in Command and Conquer 3: Tiberium Wars. Larger energy shield systems, or those powered by bigger energy sources, can absorb/dissipate more damage before failing -- so that larger starships, for example, can mount much stronger shields than a small, single-person starfighter, much in the way that a seagoing battleship has much thicker armor than a tiny patrol boat. In some instances, shields are actually able to incorporate at least some of the projectile's kinetic energy into themselves, making the shield stronger with each hit.

In some works, shields are completely invulnerable to all technology of the time, yet can only be operated for a limited period of time, or at a great expense of energy. This is often used in games to give the player temporary invulnerability (for example, the "Iron Curtain" used by the Soviet Union in Command & Conquer: Red Alert 2). In other examples, shields are invulnerable, yet they are unreliable, meaning they can't block everything. One such example is Haegemonia, where the basic deflector shields deployed in the late stages of the Earth-Mars civil war were capable of blocking projectiles with an average chance of 30% (meaning shots went right through the shield 70% of the time). This ratio was later improved, yet these shields weren't completely invulnerable; in addition, although the most advanced shields used at the beginning of the Human-Kariak-Darzok war boasted an impressive 80% blocking ratio, they were largely ineffective (only about 40%) against missile weapons, a lethal liability on planetary shields.

Very rarely, weapons designed specifically against shields also appeared (such as the "phasing cannon" in X-COM: Interceptor: it was designed to rapidly deplete the target craft's shields so that it can be finished off or disabled quickly). These pieces of equipment were designed to shut down or otherwise weaken the targeted ship/building/planet's shields so that other weapons can be brought to bear on the vulnerable hull/walls/planetary surface. An even rarer type of anti-shield weaponry include projectiles that are capable of penetrating the shield itself (notably the "Shield Breaker" round designed for use in the Exitus sniper rifle, which is in turn used by Vindicare Assassins in Warhammer 40,000, often against individuals using personal shields).

Examples

- The ability to create a force field is a popular superpower in comic books and associated media. While only a few characters have the explicit ability to create force fields (for example, the Invisible Woman and Violet Parr), many can emulate it with other powers, such as Green Lantern's energy constructs, Jean Grey's telekinesis, and Magneto's manipulation of electromagnetic fields.
- In the various Star Trek series, shields that function in an unexplained manner serve as a primary protection against weapons fire from enemy ships. Also, inside ships, force field generators can seal off ship atmosphere from the outside vacuum, in the case when a photon torpedo or phaser beam penetrates the ship's hull resulting in loose items and people being blown out to a slow and silent death.
- In the Star Wars universe, deflector shields are standard issue on most ships and perform a function similar to that of their Star Trek counterparts. Unlike Star Trek, multiple kinds

of shielding are required to guard against different weapons and interstellar debris.
- In the popular RTS Starcraft, all Protoss units and buildings are surrounding by slowly-regenerating psionic force fields, which will dissipate after taking a set amount of damage, allowing the health of the unit to be attacked directly.
- In Neon Genesis Evangelion, AT fields are explained to be simultaneously the defensive barrier generated by the Angels and Evangelions and the psychological barrier that separates the identities of different people, with the only difference between the two types being that the Angels and Evangelions can project it outwards.
- In the Dune universe, personal shields have been deployed that can stop objects with high kinetic energy. As well, when struck by an energy weapon, the subsequent reaction makes both the shield and emitter explode on a nuclear scale. In response to this, many have returned to using melee weapons, slowed before strike to penetrate the shield. Shields cannot be used on Arrakis as they attract nearby sandworms and drive them into killing frenzy. The Fremen, who are used to acting without the slow-down necessitated by the shields, take advantage of this to hurt their enemies with devastating efficiency.
- In Isaac Asimov's Foundation universe, personal shields have been developed by scientists specialising in miniaturisation. Used by Traders, they are unknown to other inhabitants of the Galactic Empire
- In the Halo Series, shielding is used by the main character's MJOLNIR powered assault armour, made by the UNSC from reverse-engineered alien technology. It can protect against projectile weapons to a large degreee, yet not so well against plasma weaponry. Hits will strain the shield and eventually deplete it, but if the wearer can stay out of the line of fire for a while, the shield will recharge back to full strength. Additionally, shields can be overcharged to absorb up to 300% damage compared to normal operating mode, at the expense that an overloaded shield can't recharge until fully depleted.
- In Sins of a Solar Empire, shields protect against all damage, but take an equivalent amount of damage. They constantly regenerate. Shields can be bypassed with Phase Missiles, tech which is exclusive to the Vasari faction. Shields, like Phase Drives, are standard equipment on all combat ships bigger than a fighter. Shields can be upgraded up to four times.
- In Outlaw Star, several characters are equipped with personal Light Shields, which absorb all but the most powerful weapons fire, but have limited power and can only be operated for seconds or minutes. The shield generator can also be overloaded and destroyed if the shield sustains too much damage.

Notes

[1] Shiga, David (2006-07-17). "Plasma bubble could protect astronauts on Mars trip" (http://www.newscientist.com/article/dn9567). *New Scientist*. Reed Business Information Ltd.. . Retrieved on 2008-12-13.
[2] Shiga, David (2007-04-18). "'Deflector' shields could protect future astronauts" (http://www.newscientist.com/article/dn11623). *New Scientist*. Reed Business Information Ltd.. . Retrieved on 2008-12-13.
[3] Rincon, Paul (2007-04-18). "Space shield to block radiation" (http://news.bbc.co.uk/2/hi/science/nature/6567709.stm). *BBC News Online*. BBC. . Retrieved on 2008-12-13.
[4] Beaty, Bill. ""Invisible Electrostatic Wall" at 3M adhesive tape plant" (http://amasci.com/weird/unusual/e-wall.html). *Science Hobbyist*. . Retrieved on 2008-12-13.

Further reading

- Andrews, Dana G. (2004-07-13). " Things to do While Coasting Through Interstellar Space (http://pdf.aiaa.org/preview/CDReadyMJPC2004_946/PV2004_3706.pdf)" (PDF) in *40th AIAA/ASME/SAE/ASEE Joint Propulsion Conference and Exhibit* (http://www.aiaa.org/agenda.cfm?lumeetingid=946).. AIAA 2004-3706. Retrieved on 2008-12-13.
- Martin, A.R. (1978). "Bombardment by Interstellar Material and Its Effects on the Vehicle, Project Daedalus Final Report". *Journal of the British Interplanetary Society*: S116-S121.

Jahn-Teller

1. redirect Jahn–Teller effect

Computational Physics and Sciences

Computational Science

1. REDIRECT Computational science

This is a redirect from a title with another method of capitalisation. It leads to the title in accordance with the Wikipedia naming conventions for capitalisation, and can help writing, searching, and international language issues.

Pages linking to any of these redirects may be updated to link directly to the target page. However, do not replace these redirected links with a piped link unless the page is updated for another reason.

For more information, see Category:Redirects from other capitalisations.

Computational Chemistry List

The **Computation Chemistry List** (CCL) was established on January 11 1991, as an independent electronic forum for chemistry researchers and educators from around the world. According to the forum's web site, it is estimated that more than 3000 members in more than 50 countries are reading CCL messages regularly, and the discussions cover all aspects of computational chemistry.[1] The list is widely supported and used by the computational chemistry community.[2] [3] [4] [5] The list also hosts many resources on computational chemistry. For example, it hosted a pre-publication version of *Computational Chemistry* by David Young.[6]

References

[1] CCL Home Page (http://www.ccl.net)
[2] Intute (http://www.intute.ac.uk/sciences/cgi-bin/fullrecord.pl?handle=2005311-183128)
[3] Sheffield Chemdex (http://www.chemdex.org/index.php?sid=656909022&cat=184&t=sub_pages)
[4] Chemistry Information on the Internet (http://hackberry.trinity.edu/cheminf.html)
[5] Wiley (http://www3.interscience.wiley.com/cgi-bin/jabout/33822/OtherResources.html?CRETRY=1&SRETRY=0)
[6] *Computational Chemistry* , David Young, Wiley-Interscience, 2001, pg xxi

Mathematical model

Note: The term model *has a different meaning in model theory, a branch of mathematical logic. An artifact which is used to illustrate a mathematical idea is also called a* mathematical model *and this usage is the reverse of the sense explained below.*

A **mathematical model** uses mathematical language to describe a system. Mathematical models are used not only in the natural sciences and engineering disciplines (such as physics, biology, earth science, meteorology, and engineering) but also in the social sciences (such as economics, psychology, sociology and political science); physicists, engineers, computer scientists, and economists use mathematical models most extensively.

Eykhoff (1974) defined a *mathematical model* as 'a representation of the essential aspects of an existing system (or a system to be constructed) which presents knowledge of that system in usable form'.[1]

Mathematical models can take many forms, including but not limited to dynamical systems, statistical models, differential equations, or game theoretic models. These and other types of models can overlap, with a given model involving a variety of abstract structures.

Examples of mathematical models

- *Population Growth*. A simple (though approximate) model of population growth is the Malthusian growth model. A slightly more realistic and largely used population growth model is the logistic function, and its extensions.
- *Model of a particle in a potential-field*. In this model we consider a particle as being a point of mass *m* which describes a trajectory which is modeled by a function $x : \mathbf{R} \to \mathbf{R}^3$ given its coordinates in space as a function of time. The potential field is given by a function V:$\mathbf{R}^3 \to \mathbf{R}$ and the trajectory is a solution of the differential equation

  $$m\frac{d^2}{dt^2}x(t) = -\operatorname{grad}(V)(x(t)).$$

  Note this model assumes the particle is a point mass, which is certainly known to be false in many cases we use this model, for example, as a model of planetary motion.
- *Model of rational behavior for a consumer*. In this model we assume a consumer faces a choice of *n* commodities labeled 1,2,...,*n* each with a market price p_1, p_2,..., p_n. The consumer is assumed to have a *cardinal* utility function *U* (cardinal in the sense that it assigns numerical values to utilities), depending on the amounts of commodities x_1, x_2,..., x_n consumed. The model further assumes that the consumer has a budget *M* which she uses to purchase a vector x_1, x_2,..., x_n in such a way as to maximize $U(x_1, x_2, ..., x_n)$. The problem of rational behavior in this model then becomes an optimization problem, that is:

  $$\max U(x_1, x_2, \ldots, x_n)$$

  subject to:

  $$\sum_{i=1}^{n} p_i x_i \leq M.$$

  $$x_i \geq 0 \quad \forall i \in \{1, 2, \ldots, n\}$$

  This model has been used in general equilibrium theory, particularly to show existence and Pareto optimality of economic equilibria. However, the fact that this particular

formulation assigns *numerical values* to levels of satisfaction is the source of criticism (and even ridicule). However, it is not an essential ingredient of the theory and again this is an idealization.

- *Neighbour-sensing model* explains the mushroom formation from the initially chaotic fungal network.

Modeling contains selecting and identifying relevant aspects of a situation in real world.

Background

Often when engineers analyze a system to be controlled or optimized, they use a mathematical model. In analysis, engineers can build a descriptive model of the system as a hypothesis of how the system could work, or try to estimate how an unforeseeable event could affect the system. Similarly, in control of a system, engineers can try out different control approaches in simulations.

A mathematical model usually describes a system by a set of variables and a set of equations that establish relationships between the variables. The values of the variables can be practically anything; real or integer numbers, boolean values or strings, for example. The variables represent some properties of the system, for example, measured system outputs often in the form of signals, timing data, counters, and event occurrence (yes/no). The actual model is the set of functions that describe the relations between the different variables.

Building blocks

There are six basic groups of variables: decision variables, input variables, state variables, exogenous variables, random variables, and output variables. Since there can be many variables of each type, the variables are generally represented by vectors.

Decision variables are sometimes known as independent variables. Exogenous variables are sometimes known as parameters or constants. The variables are not independent of each other as the state variables are dependent on the decision, input, random, and exogenous variables. Furthermore, the output variables are dependent on the state of the system (represented by the state variables).

Objectives and constraints of the system and its users can be represented as functions of the output variables or state variables. The objective functions will depend on the perspective of the model's user. Depending on the context, an objective function is also known as an index of performance, as it is some measure of interest to the user. Although there is no limit to the number of objective functions and constraints a model can have, using or optimizing the model becomes more involved (computationally).

Classifying mathematical models

Many mathematical models can be classified in some of the following ways:

1. **Linear vs. nonlinear:** Mathematical models are usually composed by variables, which are abstractions of quantities of interest in the described systems, and operators that act on these variables, which can be algebraic operators, functions, differential operators, etc. If all the operators in a mathematical model present linearity, the resulting mathematical model is defined as linear. A model is considered to be nonlinear

otherwise.
The question of linearity and nonlinearity is dependent on context, and linear models may have nonlinear expressions in them. For example, in a statistical linear model, it is assumed that a relationship is linear in the parameters, but it may be nonlinear in the predictor variables. Similarly, a differential equation is said to be linear if it can be written with linear differential operators, but it can still have nonlinear expressions in it. In a mathematical programming model, if the objective functions and constraints are represented entirely by linear equations, then the model is regarded as a linear model. If one or more of the objective functions or constraints are represented with a nonlinear equation, then the model is known as a nonlinear model.
Nonlinearity, even in fairly simple systems, is often associated with phenomena such as chaos and irreversibility. Although there are exceptions, nonlinear systems and models tend to be more difficult to study than linear ones. A common approach to nonlinear problems is linearization, but this can be problematic if one is trying to study aspects such as irreversibility, which are strongly tied to nonlinearity.

2. **Deterministic vs. probabilistic (stochastic):** A deterministic model is one in which every set of variable states is uniquely determined by parameters in the model and by sets of previous states of these variables. Therefore, deterministic models perform the same way for a given set of initial conditions. Conversely, in a stochastic model, randomness is present, and variable states are not described by unique values, but rather by probability distributions.
3. **Static vs. dynamic:** A static model does not account for the element of time, while a dynamic model does. Dynamic models typically are represented with difference equations or differential equations.
4. **Lumped vs. distributed parameters:** If the model is homogeneous (consistent state throughout the entire system) the parameters are distributed. If the model is heterogeneous (varying state within the system), then the parameters are lumped. Distributed parameters are typically represented with partial differential equations.

A priori information

Mathematical modeling problems are often classified into black box or white box models, according to how much a priori information is available of the system. A black-box model is a system of which there is no a priori information available. A white-box model (also called glass box or clear box) is a system where all necessary information is available. Practically all systems are somewhere between the black-box and white-box models, so this concept only works as an intuitive guide for approach.

Usually it is preferable to use as much a priori information as possible to make the model more accurate. Therefore the white-box models are usually considered easier, because if you have used the information correctly, then the model will behave correctly. Often the a priori information comes in forms of knowing the type of functions relating different variables. For example, if we make a model of how a medicine works in a human system, we know that usually the amount of medicine in the blood is an exponentially decaying function. But we are still left with several unknown parameters; how rapidly does the medicine amount decay, and what is the initial amount of medicine in blood? This example is therefore not a completely white-box model. These parameters have to be estimated through some means before one can use the model.

In black-box models one tries to estimate both the functional form of relations between variables and the numerical parameters in those functions. Using a priori information we could end up, for example, with a set of functions that probably could describe the system adequately. If there is no a priori information we would try to use functions as general as possible to cover all different models. An often used approach for black-box models are neural networks which usually do not make assumptions about incoming data. The problem with using a large set of functions to describe a system is that estimating the parameters becomes increasingly difficult when the amount of parameters (and different types of functions) increases.

Subjective information

Sometimes it is useful to incorporate subjective information into a mathematical model. This can be done based on intuition, experience, or expert opinion, or based on convenience of mathematical form. Bayesian statistics provides a theoretical framework for incorporating such subjectivity into a rigorous analysis: one specifies a prior probability distribution (which can be subjective) and then updates this distribution based on empirical data. An example of when such approach would be necessary is a situation in which an experimenter bends a coin slightly and tosses it once, recording whether it comes up heads, and is then given the task of predicting the probability that the next flip comes up heads. After bending the coin, the true probability that the coin will come up heads is unknown, so the experimenter would need to make an arbitrary decision (perhaps by looking at the shape of the coin) about what prior distribution to use. Incorporation of the subjective information is necessary in this case to get an accurate prediction of the probability, since otherwise one would guess 1 or 0 as the probability of the next flip being heads, which would be almost certainly wrong.[2]

Complexity

In general, model complexity involves a trade-off between simplicity and accuracy of the model. Occam's Razor is a principle particularly relevant to modeling; the essential idea being that among models with roughly equal predictive power, the simplest one is the most desirable. While added complexity usually improves the fit of a model, it can make the model difficult to understand and work with, and can also pose computational problems, including Numerical instability. Thomas Kuhn argues that as science progresses, explanations tend to become more complex before a Paradigm shift offers radical simplification.

For example, when modeling the flight of an aircraft, we could embed each mechanical part of the aircraft into our model and would thus acquire an almost white-box model of the system. However, the computational cost of adding such a huge amount of detail would effectively inhibit the usage of such a model. Additionally, the uncertainty would increase due to an overly complex system, because each separate part induces some amount of variance into the model. It is therefore usually appropriate to make some approximations to reduce the model to a sensible size. Engineers often can accept some approximations in order to get a more robust and simple model. For example Newton's classical mechanics is an approximated model of the real world. Still, Newton's model is quite sufficient for most ordinary-life situations, that is, as long as particle speeds are well below the speed of light, and we study macro-particles only.

Training

Any model which is not pure white-box contains some parameters that can be used to fit the model to the system it shall describe. If the modelling is done by a neural network, the optimization of parameters is called *training*. In more conventional modelling through explicitly given mathematical functions, parameters are determined by curve fitting.

Model evaluation

A crucial part of the modeling process is the evaluation of whether or not a given mathematical model describes a system accurately. This question can be difficult to answer as it involves several different types of evaluation.

Fit to empirical data

Usually the easiest part of model evaluation is checking whether a model fits experimental measurements or other empirical data. In models with parameters, a common approach to test this fit is to split the data into two disjoint subsets: training data and verification data. The training data are used to estimate the model parameters. An accurate model will closely match the verification data even though this data was not used to set the model's parameters. This practice is referred to as cross-validation in statistics.

Defining a metric to measure distances between observed and predicted data is a useful tool of assessing model fit. In statistics, decision theory, and some economic models, a loss function plays a similar role.

While it is rather straightforward to test the appropriateness of parameters, it can be more difficult to test the validity of the general mathematical form of a model. In general, more mathematical tools have been developed to test the fit of statistical models than models involving Differential equations. Tools from nonparametric statistics can sometimes be used to evaluate how well data fits a known distribution or to come up with a general model that makes only minimal assumptions about the model's mathematical form.

Scope of the model

Assessing the scope of a model, that is, determining what situations the model is applicable to, can be less straightforward. If the model was constructed based on a set of data, one must determine for what systems or situations the data is a typical set of data from.

The question of whether the model describes well the properties of the system between data points is called interpolation, and the same question for events or data points outside the observed data is called extrapolation.

As an example of the typical limitations of the scope of a model, in evaluating Newtonian classical mechanics, we can note that Newton made his measurements without advanced equipment, so he could not measure properties of particles travelling at speeds close to the speed of light. Likewise, he did not measure the movements of molecules and other small particles, but macro particles only. It is then not surprising that his model does not extrapolate well into these domains, even though his model is quite sufficient for ordinary life physics.

Philosophical considerations

Many types of modeling implicitly involve claims about causality. This is usually (but not always) true of models involving differential equations. As the purpose of modeling is to increase our understanding of the world, the validity of a model rests not only on its fit to empirical observations, but also on its ability to extrapolate to situations or data beyond those originally described in the model. One can argue that a model is worthless unless it provides some insight which goes beyond what is already known from direct investigation of the phenomenon being studied.

An example of such criticism is the argument that the mathematical models of Optimal foraging theory do not offer insight that goes beyond the common-sense conclusions of evolution and other basic principles of ecology.[3] .

See also

- Biologically-inspired computing
- Cliodynamics
- Computer simulation
- Differential equations
- Dynamical systems
- Model
- Model (economics)
- → Mathematical biology
- Mathematical models in physics
- Mathematical diagram
- Mathematical psychology
- Mathematical sociology
- Simulation
- Statistical model

References

[1] Eykhoff, Pieter *System Identification: Parameter and State Estimation*, Wiley & Sons, (1974). ISBN 0471249807

[2] MacKay, D.J. *Information Theory, Inference, and Learning Algorithms*, Cambridge, (2003-2004). ISBN 0521642981

[3] Optimal Foraging Theory: A Critical Review - Annual Review of Ecology and Systematics, 15(1):523 - First Page Image (http://arjournals.annualreviews.org/doi/abs/10.1146/annurev.es.15.110184.002515?journalCode=ecolsys)

Further reading

Books

- Aris, Rutherford [1978] (1994). *Mathematical Modelling Techniques*, New York : Dover. ISBN 0-486-68131-9
- Lin, C.C. & Segel, L.A. (1988). *Mathematics Applied to Deterministic Problems in the Natural Sciences*, Philadelphia : SIAM. ISBN 0-89871-229-7
- Gershenfeld, N., The Nature of Mathematical Modeling, Cambridge University Press, (1998).ISBN 0521570956

- Yang, X.-S., Mathematical Modelling for Earth Sciences, Dudedin Academic, (2008). ISBN 1903765927

Specific applications

- Peierls, Rudolf. Model-making in physics (http://www.informaworld.com/smpp/content~content=a752582770~db=all~order=page), Contemporary Physics, Volume 21 (1), January 1980, 3-17
- Korotayev A., Malkov A., Khaltourina D. (2006). *Introduction to Social Macrodynamics: Compact Macromodels of the World System Growth* (http://cliodynamics.ru/index.php?option=com_content&task=view&id=124&Itemid=70). Moscow : Editorial URSS (http://urss.ru/cgi-bin/db.pl?cp=&lang=en&blang=en&list=14&page=Book&id=34250). ISBN 5-484-00414-4

External links

General reference material

- McLaughlin, Michael P. (1999) 'A Tutorial on Mathematical Modeling' (http://www.causascientia.org/math_stat/Tutorial.pdf) PDF (264 KiB)
- Patrone, F. Introduction to modeling via differential equations (http://www.diptem.unige.it/patrone/differential_equations_intro.htm), with critical remarks.
- Plus teacher and student package: Mathematical Modelling. (http://plus.maths.org/issue44/package/index.html) Brings together all articles on mathematical modelling from *Plus*, the online mathematics magazine produced by the Millennium Mathematics Project at the University of Cambridge.

Software

- List of computer simulation software

Mathematical chemistry

Mathematical chemistry is the area of research engaged in the novel and nontrivial applications of mathematics to chemistry; it concerns itself principally with the mathematical modeling of chemical phenomena.[1] Mathematical chemistry has also sometimes been called **computer chemistry**, but should not be confused with computational chemistry.

Major areas of research in mathematical chemistry include chemical graph theory, which deals with topics such as the mathematical study of isomerism and the development of topological descriptors or indices which find application in quantitative structure-property relationships; chemical aspects of group theory, which finds applications in stereochemistry and → quantum chemistry; and topological aspects of chemistry.

The history of the approach may be traced back into 18th century. Georg Helm published a treatise titled "The Principles of Mathematical Chemistry: The Energetics of Chemical Phenomena" in 1894[2] . Some of the more contemporary periodical publications specializing in the field are MATCH Communications in Mathematical and in Computer Chemistry, first published in 1975, and the Journal of Mathematical Chemistry, first published in 1987.

The basic models for mathematical chemistry are molecular graph and topological index.

See also

- Cheminformatics
- Computational chemistry
- Combinatorial chemistry
- Molecular modeling

Bibliography

- Chemical Applications of Topology and Graph Theory, ed. by R. B. King, Elsevier, 1983.
- Mathematical Concepts in Organic Chemistry, by I. Gutman, O. E. Polansky, Springer-Verlag, Berlin, 1986.
- Mathematical Chemistry Series, ed. by D. Bonchev, D. H. Rouvray, Gordon and Breach Science Publisher, Amsterdam, 2000.

Notes

[1] A review (http://links.jstor.org/sici?sici=0036-1445(198806)30:2<348:MCIOC>2.0.CO;2-N&size=SMALL&origin=JSTOR-reducePage) of the book by Ivan Gutman, Oskar E. Polansky, "Mathematical Concepts in Organic Chemistry" in *SIAM Review* Vol. 30, No. 2 (1988), pp. 348-350

[2] Helm, Georg. The Principles of Mathematical Chemistry: The Energetics of Chemical Phenomena. translated by J. Livingston R. Morgan. New York: John Wiley & Sons, 1897. (http://books.google.com/books?hl=en&id=cyUuAAAAYAAJ&dq=helm+mathematical+chemistry&printsec=frontcover&source=web&ots=_0vgt-Wots&sig=w4EkV9aqaFd2jb6dXOOs3XObc9o&sa=X&oi=book_result&resnum=1&ct=result#PPP9,M1)

References

- N. Trinajstić, I. Gutman, Mathematical Chemistry, Croatica Chemica Acta, 75(2002), pp. 329-356.
- A. T. Balaban, Reflections about Mathematical Chemistry, Foundations of Chemistry, 7(2005), pp. 289-306.

External links

- Journal of Mathematical Chemistry (http://www.springerlink.com/content/101749/)
- MATCH Communications in Mathematical and in Computer Chemistry (http://www.pmf.kg.ac.yu/match/)

Molecular graphics

Molecular graphics (**MG**) is the discipline and philosophy of studying molecules and their properties through graphical representation.[1] IUPAC limits the definition to representations on a "graphical display device".[2] Ever since Dalton's atoms and Kekule's benzene, there has been a rich history of hand-drawn atoms and molecules, and these representations have had an important influence on modern molecular graphics. This article concentrates on the use of computers to create molecular graphics. Note, however, that many molecular graphics programs and systems have close coupling between the graphics and editing commands or calculations such as in → molecular modelling.

Relation to molecular models

There has been a long tradition of creating molecular models from physical materials. Perhaps the best known is Crick and Watson's model of DNA built from rods and planar sheets, but the most widely used approach is to represent all atoms and bonds explicitly using the "ball and stick" approach. This can demonstrate a wide range of properties, such as shape, relative size, and flexibility. Many chemistry courses expect that students will have access to ball and stick models. One goal of mainstream molecular graphics has been to represent the "ball and stick" model as realistically as possible and to couple this with calculations of molecular properties.

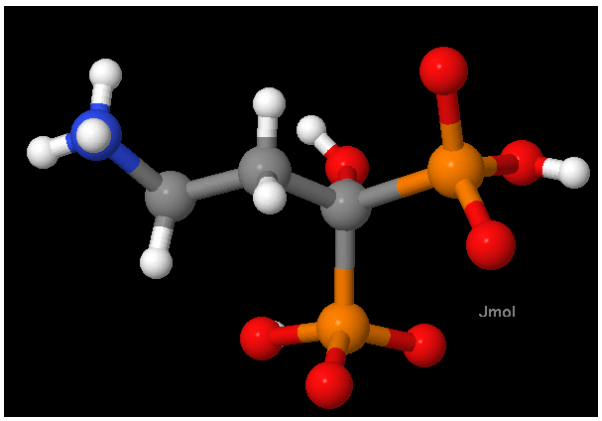


Fig. 1. Key: Hydrogen = white, carbon = grey, nitrogen = blue, oxygen = red, and phosphorus = orange.

Figure 1 shows a small molecule ($NH_3CH_2CH_2C(OH)(PO_3H)(PO_3H)$-), as drawn by the Jmol program. It is important to realise that the colours are purely a convention. Molecules can never be visible under any light microscope and atoms are not coloured, do not have hard surfaces and do not reflect light. Bonds are not rod-shaped. If physical molecular models had not existed, it is unlikely that molecular graphics would currently use this metaphor.

Comparison of physical models with molecular graphics

Physical models and computer models have partially complementary strengths and weaknesses. Physical models can be used by those without access to a computer and now can be made cheaply out of plastic materials. Their tactile and visual aspects cannot be easily reproduced by computers (although haptic devices have occasionally been built). On a computer screen, the flexibility of molecules is also difficult to appreciate; illustrating the pseudorotation of cyclohexane is a good example of the value of mechanical models.

However, it is difficult to build large physical molecules, and all-atom physical models of even simple proteins could take weeks or months to build. Moreover, physical models are not robust and they decay over time. Molecular graphics is particularly valuable for representing global and local properties of molecules, such as electrostatic potential. Graphics can also be animated to represent molecular processes and chemical reactions, a feat that is not easy to reproduce physically.

History

Initially the rendering was on early CRT screens or through plotters drawing on paper. Molecular structures have always been an attractive choice for developing new computer graphics tools, since the input data are easy to create and the results are usually highly appealing. The first example of MG was a display of a protein molecule (Project MAC, 1966) by Cyrus Levinthal and Robert Langridge. Among the milestones in high-performance MG was the work of Nelson Max in "realistic" rendering of macromolecules using reflecting spheres.

By about 1980 many laboratories both in academia and industry had recognized the power of the computer to analyse and predict the properties of molecules, especially in materials science and the pharmaceutical industry. The discipline was often called "molecular graphics" and in 1982 a group of academics and industrialists in the UK set up the Molecular Graphics Society (MGS). Initially much of the technology concentrated either on high-performance 3D graphics, including interactive rotation or 3D rendering of atoms as spheres (sometimes with radiosity). During the 1980s a number of programs for calculating molecular properties (such as → molecular dynamics and quantum mechanics) became available and the term "molecular graphics" often included these. As a result the MGS has now changed its name to the Molecular Graphics and Modelling Society (MGMS).

The requirements of macromolecular crystallography also drove MG because the traditional techniques of physical model-building could not scale. Alwyn Jones' FRODO program (and later "O") were developed to overlay the molecular electron density determined from X-ray crystallography and the hypothetical molecular structure.

Art, science and technology in molecular graphics

Both computer technology and graphic arts have contributed to molecular graphics. The development of structural biology in the 1950s led to a requirement to display molecules with thousands of atoms. The existing computer technology was limited in power, and in any case a naive depiction of all atoms left viewers overwhelmed. Most systems therefore used conventions where information was implicit or stylistic. Two vectors meeting at a point implied an atom or (in macromolecules) a complete residue (10-20 atoms).

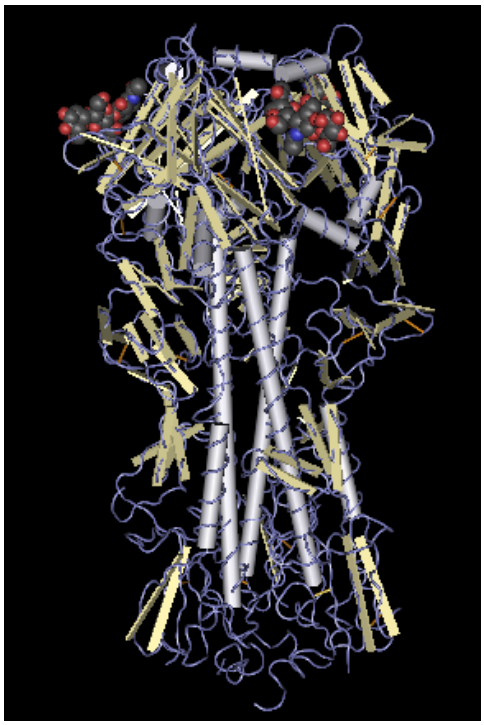


Fig. 2. Image of hemagglutinin with alpha helices depicted as cylinders and the rest of the chain as silver coils. The individual protein atoms (several thousand) have been hidden. All of the non-hydrogen atoms in the two ligands (presumably sialic acid) have been shown near the top of the diagram. Key: Carbon = grey, oxygen = red, nitrogen = blue.

The macromolecular approach was popularized by Dickerson and Geis' presentation of proteins and the graphic work of Jane Richardson through high-quality hand-drawn diagrams such as the "ribbon" representation. In this they strove to capture the intrinsic 'meaning' of the molecule. This search for the "messages in the molecule" has always accompanied the increasing power of computer graphics processing. Typically the depiction would concentrate on specific areas of the molecule (such as the active site) and this might have different colours or more detail in the number of explicit atoms or the type of depiction (e.g., spheres for atoms).

In some cases the limitations of technology have led to serendipitous methods for rendering. Most early graphics devices used vector graphics, which meant that rendering spheres and surfaces was impossible. Michael Connolly's program "MS" calculated points on the surface-accessible surface of a molecule, and the points were rendered as dots with good visibility using the new vector graphics technology, such as the Evans and Sutherland PS300 series. Thin sections ("slabs") through the structural display showed very clearly the complementarity of the surfaces for molecules binding to active sites, and the "Connolly surface" became a universal metaphor.

The relationship between the art and science of molecular graphics is shown in the exhibitions [3] sponsored by the Molecular Graphics Society. Some exhibits are created with molecular graphics programs alone, while others are collages, or involve physical materials. An example from Mike Hann (1994), inspired by Magritte's painting *Ceci n'est pas une pipe*, uses an image of a salmeterol molecule.

"*Ceci n'est pas une molecule*," writes Mike Hann, "serves to remind us that all of the graphics images presented here are not molecules, not even pictures of molecules, but pictures of icons which we believe represent some aspects of the molecule's properties."

Space-filling models

Fig. 4 is a "space-filling" representation of formic acid, where atoms are drawn to suggest the amount of space they occupy. This is necessarily an icon: in the quantum mechanical representation of molecules, there are only (positively charged) nuclei and a "cloud" of negative electrons. The electron cloud defines an approximate size for the molecule, though there can be no single precise definition of size. For many years the size of atoms has been approximated by mechanical models (CPK), where the atoms have been represented by plastic spheres whose radius (van der Waals radius) describes a sphere within which "most" of the electron density can be found. These spheres could be clicked together to show the steric aspects of the molecule rather than the positions of the nuclei. Fig. 4 shows the intricacy required to make sure that all spheres intersect correctly, and also demonstrates a reflective model.

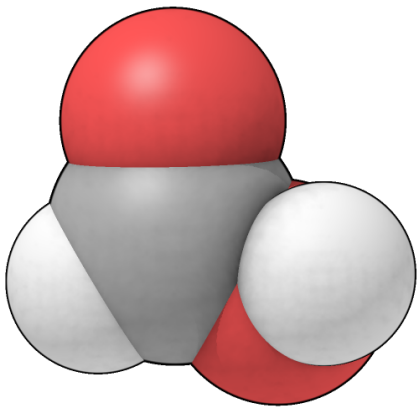


Fig. 4. Space-filling model of formic acid. Key: Hydrogen = white, carbon = black, oxygen = red.

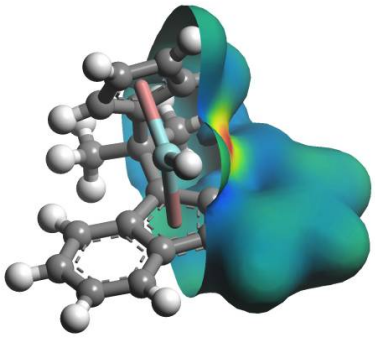


Fig. 5. A molecule (zirconocene) where part (left) is rendered as ball-and-stick and part (right) as an isosurface.

Since the atomic radii (e.g. in Fig. 4) are only slightly less than the distance between bonded atoms, the iconic spheres intersect, and in the CPK models, this was achieved by planar truncations along the bonding directions, the section being circular. When raster graphics became affordable, one of the common approaches was to replicate CPK models *in silico*. It is relatively straightforward to calculate the circles of intersection, but more complex to represent a model with hidden surface removal. A useful side product is that a conventional value for the molecular volume can be calculated.

The use of spheres is often for convenience, being limited both by graphics libraries and the additional effort required to compute complete electronic density or other space-filling quantities. It is now relatively common to see images of isosurfaces that have been coloured to show quantities such as electrostatic potential. The commonest isosurfaces are the Connolly surface, or the volume within which a given proportion of the electron density lies. The isosurface in Fig. 5 appears to show the electrostatic potential, with blue colours being negative and red/yellow (near the metal) positive. (There is no absolute convention of colouring, and red/positive, blue/negative are often confusingly reversed!) Opaque isosurfaces do not allow the atoms to be seen and identified and it is not easy to deduce them. Because of this, isosurfaces are often drawn with a degree of transparency.

Technology

Molecular graphics has always pushed the limits of display technology, and has seen a number of cycles of integration and separation of compute-host and display. Early systems like Project MAC were bespoke and unique, but in the 1970s the MMS-X and similar systems used (relatively) low-cost terminals, such as the Tektronix 4014 series, often over dial-up lines to multi-user hosts. The devices could only display static pictures but, were able to evangelize MG. In the late 1970s, it was possible for departments (such as crystallography) to afford their own hosts (e.g., PDP-11) and to attach a display (such as Evans & Sutherland's MPS) directly to the bus. The display list was kept on the host, and interactivity was good since updates were rapidly reflected in the display—at the cost of reducing most machines to a single-user system.

In the early 1980s, Evans & Sutherland (E&S) decoupled their PS300 display, which contained its own display information transformable through a dataflow architecture. Complex graphical objects could be downloaded over a serial line (e.g. 9600 baud) and then manipulated without impact on the host. The architecture was excellent for high performance display but very inconvenient for domain-specific calculations, such as electron-density fitting and energy calculations. Many crystallographers and modellers spent arduous months trying to fit such activities into this architecture.

The benefits for MG were considerable, but by the later 1980s, UNIX workstations such as Sun-3 with raster graphics (initially at a resolution of 256 by 256) had started to appear. Computer-assisted drug design in particular required raster graphics for the display of computed properties such as atomic charge and electrostatic potential. Although E&S had a high-end range of raster graphics (primarily aimed at the aerospace industry) they failed to respond to the low-end market challenge where single users, rather than engineering departments, bought workstations. As a result the market for MG displays passed to Silicon Graphics, coupled with the development of minisupercomputers (e.g., CONVEX and Alliant) which were affordable for well-supported MG laboratories. Silicon Graphics provided a graphics language, IrisGL, which was easier to use and more productive than the PS300 architecture. Commercial companies (e.g., Biosym, Polygen/MSI) ported their code to Silicon Graphics, and by the early 1990s, this was the "industry standard".

Stereoscopic displays were developed based on liquid crystal polarized spectacles, and while this had been very expensive on the PS300, it now became a commodity item. A common alternative was to add a polarizable screen to the front of the display and to provide viewers with extremely cheap spectacles with orthogonal polarization for separate eyes. With projectors such as Barco, it was possible to project stereoscopic display onto special silvered screens and supply an audience of hundreds with spectacles. In this way molecular graphics became universally known within large sectors of chemical and biochemical science, especially in the pharmaceutical industry. Because the backgrounds of many displays were black by default, it was common for modelling sessions and lectures to be held with almost all lighting turned off.

In the last decade almost all of this technology has become commoditized. IrisGL evolved to OpenGL so that molecular graphics can be run on any machine. In 1992, Roger Sayle released his RasMol program into the public domain. RasMol contained a very high-performance molecular renderer that ran on Unix/X Window, and Sayle later ported this to the Windows and Macintosh platforms. The Richardsons developed kinemages and the Mage software, which was also multi-platform. By specifying the chemical MIME type,

molecular models could be served over the Internet, so that for the first time MG could be distributed at zero cost regardless of platform. In 1995, Birkbeck College's crystallography department used this to run "Principles of Protein Structure", the first multimedia course on the Internet, which reached 100 to 200 scientists.

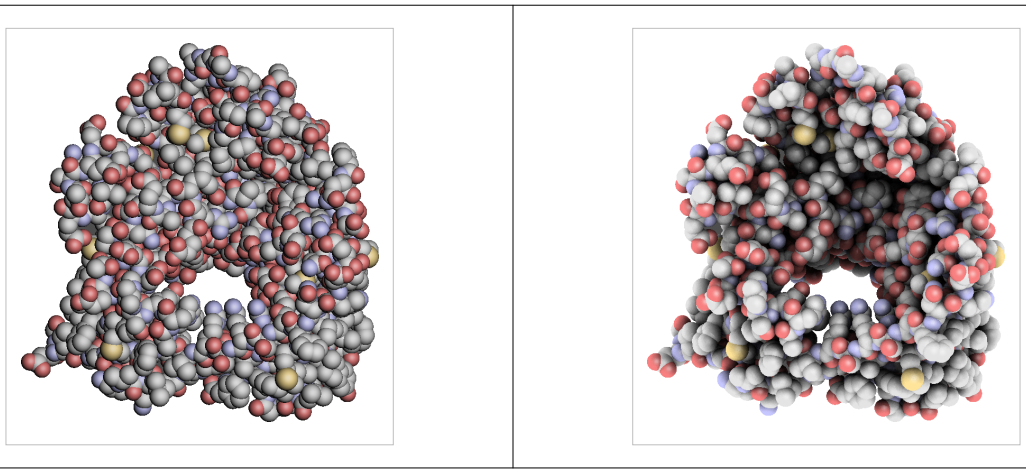


Fig. 6. A molecule of Porin (protein) shown without ambient occlusion (left) and with (right). Advanced rendering effects can improve the comprehension of the 3D shape of a molecule.

MG continues to see innovation that balances technology and art, and currently zero-cost or open source programs such as PyMOL and Jmol have very wide use and acceptance.

Recently the wide spread diffusion of advanced graphics hardware, has improved the rendering capabilities of the visualization tools. The capabilities of current shading languages allow the inclusion of advanced graphic effects (like ambient occlusion, cast shadows and non-photorealistic rendering techniques) in the interactive visualization of molecules. These graphic effects, beside being eye candy, can improve the comprehension of the three dimensional shapes of the molecules. An example of the effects that can be achieved exploiting recent graphics hardware can be seen in the simple open source visualization system QuteMol.

Algorithms

Reference frames

Drawing molecules requires a transformation between molecular coordinates (usually, but not always, in Angstrom units) and the screen. Because many molecules are chiral it is essential that the handedness of the system (almost always right-handed) is preserved. In molecular graphics the origin (0, 0) is usually at the lower left, while in many computer systems the origin is at top left. If the z-coordinate is out of the screen (towards the viewer) the molecule will be referred to right-handed axes, while the screen display will be left-handed.

Molecular transformations normally require:

- scaling of the display (but not the molecule).
- translations of the molecule and objects on the screen.
- rotations about points and lines.

Conformational changes (e.g. rotations about bonds) require rotation of one part of the molecule relative to another. The programmer must decide whether a transformation on the

screen reflects a change of view or a change in the molecule or its reference frame.

Simple

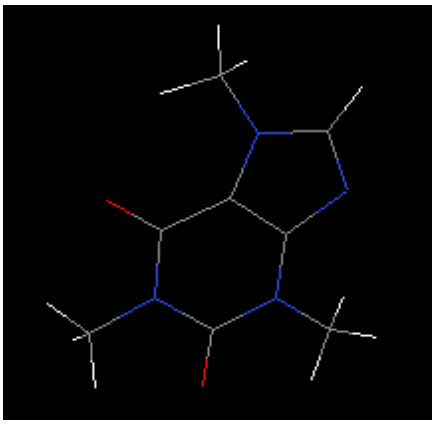


Fig. 7. Stick model of caffeine drawn in Jmol.

In early displays only vectors could be drawn e.g. (Fig. 7) which are easy to draw because no rendering or hidden surface removal is required.

On vector machines the lines would be smooth but on raster devices Bresenham's algorithm is used (note the "jaggies" on some of the bonds, which can be largely removed with antialiasing software.)

Atoms can be drawn as circles, but these should be sorted so that those with the largest z-coordinates (nearest the screen) are drawn last. Although imperfect, this often gives a reasonably attractive display. Other simple tricks which do not include hidden surface algorithms are:

- colouring each end of a bond with the same colour as the atom to which it is attached (Fig. 7).
- drawing less than the whole length of the bond (e.g. 10%-90%) to simulate the bond sticking out of a circle.
- adding a small offset white circle within the circle for an atom to simulate reflection.

Typical pseudocode for creating Fig. 7 (to fit the molecule exactly to the screen):

```
// assume:
// atoms with x, y, z coordinates (Angstrom) and elementSymbol
// bonds with pointers/references to atoms at ends
// table of colours for elementTypes
// find limits of molecule in molecule coordinates as xMin, yMin, xMax,
 yMax
scale = min(xScreenMax/(xMax-xMin), yScreenMax/(yMax-yMin))
xOffset = -xMin * scale; yOffset = -yMin * scale
for (bond in $bonds) {
  atom0 = bond.getAtom(0)
  atom1 = bond.getAtom(1)
  x0 = xOffset+atom0.getX()*scale; y0 = yOffset+atom0.getY()*scale //
(1)
  x1 = xOffset+atom1.getX()*scale; y1 = yOffset+atom1.getY()*scale //
(2)
  x1 = atom1.getX();  y1 = atom1.getY()
  xMid = (x0 + x1) /2;  yMid = (y0 + y1) /2;
  colour0 = ColourTable.getColour(atom0.getSymbol())
  drawLine (colour0, x0, y0, xMid, yMid)
  colour1 = ColourTable.getColour(atom1.getSymbol())
  drawLine (colour1, x1, y1, xMid, yMid)
}
```

Note that this assumes the origin is in the bottom left corner of the screen, with Y up the screen. Many graphics systems have the origin at the top left, with Y down the screen. In this case the lines (1) and (2) should have the y coordinate generation as:

```
y0 = yScreenMax -(yOffset+atom0.getY()*scale) // (1)
y1 = yScreenMax -(yOffset+atom1.getY()*scale) // (2)
```

Changes of this sort change the handedness of the axes so it is easy to reverse the chirality of the displayed molecule unless care is taken.

Advanced

For greater realism and better comprehension of the 3D structure of a molecule many computer graphics algorithms can be used. For many years molecular graphics has stressed the capabilities of graphics hardware and has required hardware-specific approaches. With the increasing power of machines on the desktop, portability is more important and programs such as Jmol have advanced algorithms that do not rely on hardware. On the other hand recent graphics hardware is able to interactively render very complex molecule shapes with a quality that would not be possible with standard software techniques.

Chronology

This table provides an incomplete chronology of molecular graphics advances.

Developer(s)	Approximate date	Technology	Comments
Crystallographers	< 1960	Hand-drawn	Crystal structures, with hidden atom and bond removal. Often clinographic projections.
Cyrus Levinthal, Bob Langridge	1960s	CRT	First protein display on screen (Project MAC).
Johnson, Motherwell	ca 1970	Pen plotter	ORTEP, PLUTO. Very widely deployed for publishing crystal structures.
Langridge, White, Marshall	Late 1970s	Departmental systems (PDP-11, Tektronix displays or DEC-VT11, e.g. MMS-X)	Mixture of commodity computing with early displays.
T. Alwyn Jones	1978	FRODO	Crystallographic structure solution.
Davies, Hubbard	Mid-1980s	CHEM-X, HYDRA	Laboratory systems with multicolor, raster and vector devices (Sigmex, PS300).
Biosym, Tripos, Polygen	Mid-1980s	PS300 and lower cost dumb terminals (VT200, SIGMEX)	Commercial integrated modelling and display packages.
Silicon Graphics, Sun	Late 1980s	IRIS GL (UNIX) workstations	Commodity-priced single-user workstations with stereoscopic display.
EMBL - WHAT IF [4]	1989, 2000	Machine independent	Nearly free, multifunctional, still fully supported, many free servers [5] based on it
Sayle, Richardson	1992, 1993	RasMol, Kinemage	Platform-independent MG.

MDL (van Vliet, Maffett, Adler, Holt)	1995-1998	Chime	proprietary C++ ; free browser plugin for Mac (OS9) and PCs
ChemAxon	1998-	MarvinSketch [6] & MarvinView [7] MarvinSpace [8] (2005)	proprietary Java applet or stand-alone application.
Community efforts	2000-	Jmol, PyMol, Protein Workshop (www.pdb.org)	Open-source Java applet or stand-alone application.
San Diego Supercomputer Center	2006-	Sirius	Free for academic/non-profit institutions
NOCH	2002-	NOC [9]	Powerful and open source code molecular structure explorer
Weizmann Institute of Science - Community efforts	2008-	Proteopedia	Collaborative, 3D wiki encyclopedia of proteins & other molecules

References

[1] Dickerson, R.E.; Geis, I. (1969). *The structure and action of proteins*. Menlo Park, CA: W.A. Benjamin.
[2] International Union of Pure and Applied Chemistry (1997). " molecular graphics (http://goldbook.iupac.org/MT06970.html)". *Compendium of Chemical Terminology* Internet edition.
[3] http://www.scripps.edu/mb/goodsell/mgs_art/
[4] http://swift.cmbi.ru.nl/whatif/
[5] http://swift.cmbi.ru.nl/
[6] http://www.chemaxon.com/product/msketch.html
[7] http://www.chemaxon.com/product/mview.html
[8] http://www.chemaxon.com/product/mspace.html
[9] http://noch.sourceforge.net

See also

- Molecular Design software
- Molecular model
- → Molecular modelling
- Molecular geometry
- Software for molecular mechanics modeling

External links

- The PyMOL Molecular Graphics System (http://pymol.sf.net) -- open source
  - PyMOLWiki (http://pymolwiki.org) -- community supported wiki for PyMOL
- History of Visualization of Biological Macromolecules (http://www.umass.edu/microbio/rasmol/history.htm) by Eric Martz and Eric Francoeur.
- Brief History of Molecular Mechanics/Graphics (http://stanley.chem.lsu.edu/webpub/7770-Lecture-1-intro.pdf) in LSU CHEM7770 lecture notes.
- Historical slides (http://luminary.stanford.edu/langridge/slides.htm) from Robert (Bob) Langridge. These show the influence of Crick and Watson on molecular graphics (including Levinthal's) and the development of early display technology, finishing with displays which were common in the mid-1980s on machines such as Evans and Sutherland's PS300 series.

- Interview with Langridge. (http://luminary.stanford.edu/langridge/langridge.html) The display looking down the axis of B-DNA has been likened to a rose window.
- Nelson Max's home page (http://accad.osu.edu/~waynec/history/tree/max.html) with links to 1982 classics.
- Jmol home page (http://jmol.sourceforge.net/) contains an applet with an automatic display of many features of molecular graphics including metaphors, scripting, annotation and animation.
- Richardson Lab (http://kinemage.biochem.duke.edu/) includes Kinemage and molecular graphics images.
- History of RasMol. (http://www.openrasmol.org/history.html)
- Molecule of the Month (http://www.rcsb.org/pdb/static.do?p=education_discussion/molecule_of_the_month/index.html) at RCSB/PDB.
- xeo (http://sourceforge.net/projects/xeo) xeo is a free (GPL) open project management for nanostructures using Java
- Exhibitions of Molecular Graphics Art (http://www.scripps.edu/mb/goodsell/mgs_art/), 1994, 1998.
- NOCH home page (http://noch.sourceforge.net) A powerful, efficient and open source molecular graphics tool.
- eMovie (http://www.weizmann.ac.il/ISPC/eMovie.html): a tool for creation of molecular animations with PyMOL.
- Proteopedia (http://www.proteopedia.org): The collaborative, 3D encyclopedia of proteins and other molecules.
- Ascalaph Graphics (http://www.agilemolecule.com/Ascalaph/Ascalaph_Graphics.html): a molecular viewer with some geometry editing capabilities.
- Molecular Graphics and Modelling Society. (http://www.mgms.org/)
- *Journal of Molecular Graphics and Modelling* (http://www.sciencedirect.com/science?_ob=JournalURL&_cdi=5260&_auth=y&_acct=C000053194&_version=1&_urlVersion=0&_userid=1495569&md5=1e86bcce088e98890cea52f6eda84b64) (formally *Journal of Molecular Graphics*). This journal is not open access.

Complex Systems Dynamics

Complex dynamics

Complex dynamics the study of dynamical systems for which the phase space is a complex manifold. **Complex analytic dynamics** specifies more precisely that it is analytic functions whose dynamics it is to study.

Technics[1]

- Montel's theorem
- Poincare metric
- Schwarz lemma
- Riemann mapping theorem
- → Carathéodory's theorem (conformal mapping)

See also

- complex analysis
- Orbit portrait
- John Milnor
- Complex quadratic polynomial
- Fatou set
- Julia set
- Mandelbrot set

References

[1] The Mandelbrot Set, Theme and Variations (London Mathematical Society Lecture Note Series) (No 274) by Tan Lei (Editor), Cambridge University Press, 2000

Topological dynamics

In mathematics, **topological dynamics** is a branch of the theory of dynamical systems in which qualitative, asymptotic properties of dynamical systems are studied from the viewpoint of general topology.

Scope

The central object of study in topological dynamics is a **topological dynamical system**, i.e. a topological space, together with a continuous transformation, a continuous flow, or more generally, a semigroup of continuous transformations of that space. The origins of topological dynamics lie in the study of asymptotical properties of trajectories of systems of autonomous ordinary differential equations, in particular, the behavior of limit sets and various manifestations of "repetetiveness" of the motion, such as periodic trajectories, recurrence and minimality, stability, non-wandering points. George Birkhoff is considered to be the founder of the field. A structure theorem for minimal distal flows proved by Hillel Furstenberg in the early 1960s inspired much work on classification of minimal flows. A lot of research in the 1970s and 1980s was devoted to topological dynamics of one-dimensional maps, in particular, piecewise linear self-maps of the interval and the circle.

Unlike the theory of smooth dynamical systems, where the main object of study is a smooth manifold with a diffeomorphism or a smooth flow, phase spaces considered in topological dynamics are general metric spaces (usually, compact). This necessitates development of entirely different techniques but allows extra degree of flexibility even in the smooth setting, because invariant subsets of a manifold are frequently very complicated topologically (cf limit cycle, strange attractor); additionally, shift spaces arising via symbolic representations can be considered on an equal footing with more geometric actions. Topological dynamics has intimate connections with ergodic theory of dynamical systems, and many fundamental concepts of the latter have topological analogues (cf Kolmogorov–Sinai entropy and topological entropy).

See also

- Poincaré–Bendixson theorem
- Symbolic dynamics
- → Topological conjugacy

References

- D.V.Anosov (2001), "Topological dynamics" [1], in Hazewinkel, Michiel, *Encyclopaedia of Mathematics*, Kluwer Academic Publishers, ISBN 978-1556080104
- *Topological dynamics* [2] at Scholarpedia, curated by Joseph Auslander.
- Robert Ellis, *Lectures on topological dynamics*. W. A. Benjamin, Inc., New York 1969
- Walter Gottschalk, Gustav Hedlund, *Topological dynamics*. American Mathematical Society Colloquium Publications, Vol. 36. American Mathematical Society, Providence, R. I., 1955
- J. de Vries, *Elements of topological dynamics*. Mathematics and its Applications, 257. Kluwer Academic Publishers Group, Dordrecht, 1993 ISBN 0-7923-2287-8

References

[1] http://eom.springer.de/T/t093030.htm
[2] http://www.scholarpedia.org/article/Topological_dynamics

Topological conjugacy

In mathematics, two functions are said to be **topologically conjugate** to one another if there exists a homeomorphism that will conjugate the one into the other. Topological conjugacy is important in the study of iterated functions and more generally dynamical systems, since, if the dynamics of one iterated function can be solved, then those for any topologically conjugate function follow trivially.

To illustrate this directly: suppose that *f* and *g* are iterated functions, and there exists an *h* such that

$$g = h^{-1} \circ f \circ h,$$

so that *f* and *g* are topologically conjugate. Then of course one must have

$$g^n = h^{-1} \circ f^n \circ h,$$

and so the iterated systems are conjugate as well. Here, $\circ$ denotes function composition.

As examples, the logistic map and the tent map are topologically conjugate. Furthermore, the logisitic map of unit height and the Bernoulli map are topologically conjugate.

Definition

Let X and Y be topological spaces, and let $f: X \to X$ and $g: Y \to Y$ be continuous functions. We say that f is **topologically semiconjugate** to g, if there exists a continuous surjection $h: Y \to X$ such that $f \circ h = h \circ g$. If h is a homeomorphism, then we say that f and g are **topologically conjugate**, and we call h a **topological conjugation** between f and g.

Similarly, a flow φ on X is topologically semiconjugate to a flow ψ on Y if there is a continuous surjection $h: Y \to X$ such that $\varphi(h(y), t) = h\psi(y, t)$ for each $y \in Y$, $t \in \mathbb{R}$. If h is a homeomorphism then ψ and φ are topologically conjugate.

Discussion

Topological conjugation defines an equivalence relation in the space of all continuous surjections of a topological space to itself, by declaring f and g to be related if they are topologically conjugate. This equivalence relation is very useful in the theory of dynamical systems, since each class contains all functions which share the same dynamics from the topological viewpoint. For example, orbits of g are mapped to homeomorphic orbits of f through the conjugation. Writing $g = h^{-1} \circ f \circ h$ makes this fact evident: $g^n = h^{-1} \circ f^n \circ h$. Speaking informally, topological conjugation is a “change of coordinates” in the topological sense.

However, the analogous definition for flows is somewhat restrictive. In fact, we are requiring the maps $\varphi(\cdot, t)$ and $\psi(\cdot, t)$ to be topologically conjugate for each t, which is requiring more than simply that orbits of φ be mapped to orbits of ψ homeomorphically. This motivates the definition of **topological equivalence**, which also partitions the set of all flows in X into classes of flows sharing the same dynamics, again from the topological

viewpoint.

Topological equivalence

We say that ψ and φ are **topologically equivalent**, if there is a homeomorphism $h : Y \to X$, mapping orbits of ψ to orbits of φ homeomorphically, and preserving orientation of the orbits. In other words, letting $\mathcal{O}$ denote an orbit, one has

$$h(\mathcal{O}(y,\psi)) = \{h(\psi(y,t)) : t \in \mathbb{R}\} = \{\varphi(h(y),t) : t \in \mathbb{R}\} = \mathcal{O}(h(y),\varphi)$$

for each $y \in Y$. In addition, one must line up the flow of time: for each $y \in Y$, there exists a $\delta > 0$ such that, if $0 < |s| < t < \delta$, and if s is such that $\varphi(h(y),s) = h(\psi(y,t))$, then $s > 0$.

Overall, topological equivalence is a weaker equivalence criterion than topological conjugacy, as it does not require that the time term is mapped along with the orbits and their orientation. An example of a topologically equivalent but not topologically conjugate system would be the non-hyperbolic class of two dimensional systems of differential equations that have closed orbits. While the orbits can be transformed each other to overlap in the spatial sense, the periods of such systems cannot be analogously matched, thus failing to satisfy the topological conjugacy criterion while satisfying the topological equivalence criterion.

Generalizations of dynamic topological conjugacy

There are two reported extensions of the concept of dynamic topological conjugacy:

1. Analogous systems defined as isomorphic dynamical systems

2. Adjoint dynamical systems defined via adjoint functors and natural equivalences in categorical dynamics[1] [2] .

Cited References

[1] http://planetphysics.org/encyclopedia/Complexity.html Complexity and Categorical Dynamics

[2] http://planetphysics.org/encyclopedia/AnalogousSystems3.html Analogous systems, Topological Conjugacy and Adjoint Systems

See also

- Commutative diagram

This article incorporates material from topological conjugation on PlanetMath, which is licensed under the GFDL.

Network dynamics

Network dynamics is the study of networks that change in time. These networks could be from the fields of biology,sociology,economics,computer science,graph theory etc.

For a dynamical systems approach to network dynamics, see sequential dynamical system.

See also

- → Dynamic network analysis
- → Metastability in the brain
- Gaussian network model
- Neural network
- Cellular neural network
- Small-world network
- Network planning and design
- Dynamic Bayesian network
- Dynamic single-frequency networks
- Biological network inference
- Technology Dynamics
- Source-sink dynamics
- Social network analysis software

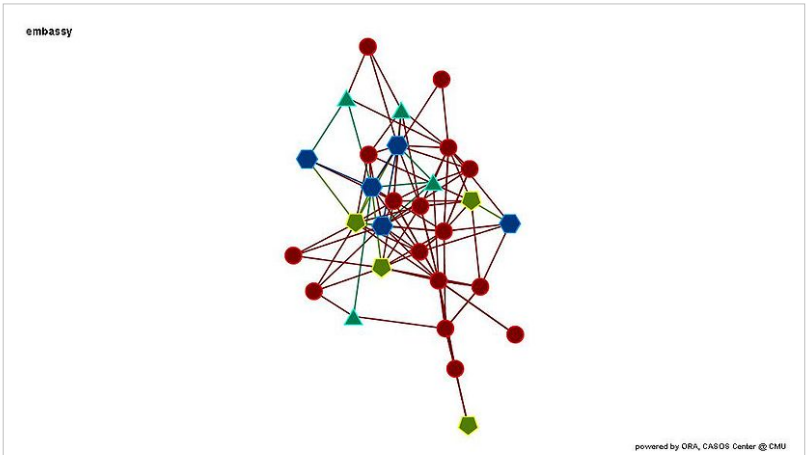
Dynamic network analysis

Dynamic network analysis (DNA) is an emergent scientific field that brings together traditional social network analysis (SNA), link analysis (LA) and multi-agent systems (MAS). There are two aspects of this field. The first is the statistical analysis of DNA data. The second is the utilization of simulation to address issues of network dynamics. DNA networks vary from traditional social networks in that they are larger, dynamic, multi-mode, multi-plex networks, and may contain varying levels of uncertainty.

DNA statistical tools are generally optimized for large-scale networks and admit the analysis of multiple networks simultaneously in which, there are multiple types of nodes (multi-node) and multiple types of links (multi-plex). In contrast, SNA statistical tools focus on single or at most two mode data and facilitate the analysis of only one type of link at a time.

DNA statistical tools tend to provide more measures to the user, because they have measures that use data drawn from multiple networks simultaneously. From a computer simulation perspective, nodes in DNA are like atoms in quantum theory, nodes can be, though need not be, treated as probabilistic. Whereas nodes in a traditional SNA model are static, nodes in a DNA model have the ability to learn. Properties change over time; nodes can adapt: A company's employees can learn new skills and increase their value to the network; Or, capture one terrorist and three more are forced to improvise. Change propagates from one node to the next and so on. DNA adds the element of a network's evolution and considers the circumstances under which change is likely to occur.

Illustrative problems that people in the DNA area work on



An example of a multi-entity, multi-network, dynamic network diagram

- Developing metrics and statistics to assess and identify change within and across networks.
- Developing and validating simulations to study network change, evolution, adaptation, decay... See Computer simulation and organizational studies
- Developing and validating formal models of network generation and evolution
- Developing and testing theory of network change, evolution, adaptation, decay...
- Developing techniques to visualize network change overall or at the node or group level
- Developing statistical techniques to see whether differences observed over time in networks are due to simply different samples from a distribution of links and nodes or changes over time in the underlying distribution of links and nodes
- Developing control processes for networks over time
- Developing algorithms to change distributions of links in networks over time
- Developing algorithms to track groups in networks over time.
- Developing tools to extract or locate networks from various data sources such as texts.
- Developing statistically valid measurements on networks over time.
- Examining the robustness of network metrics under various types of missing data
- Empirical studies of multi-mode multi-link multi-time period networks
- Examining networks as probabilistic time-variant phenomena
- Forecasting change in existing networks
- Identifying trails through time given a sequence of networks.
- Identifying changes in node criticality given a sequence of networks anything else related to multi-mode multi-link multi-time period networks.

Kathleen Carley, of Carnegie Mellon University, is the leading authority in this field.

Further reading

- Kathleen M. Carley, 2003, “Dynamic Network Analysis” in Dynamic Social Network Modeling and Analysis: Workshop Summary and Papers, Ronald Breiger, Kathleen Carley, and Philippa Pattison, (Eds.) Committee on Human Factors, National Research Council, National Research Council. Pp. 133–145, Washington, DC.
- Kathleen M. Carley, 2002, “Smart Agents and Organizations of the Future” The Handbook of New Media. Edited by Leah Lievrouw and Sonia Livingstone, Ch. 12, pp. 206–220, Thousand Oaks, CA, Sage.
- Kathleen M. Carley, Jana Diesner, Jeffrey Reminga, Maksim Tsvetovat, 2008, Toward an Interoperable Dynamic Network Analysis Toolkit, DSS Special Issue on Cyberinfrastructure for Homeland Security: Advances in Information Sharing, Data Mining, and Collaboration Systems. Decision Support Systems [1] 43(4):1324-1347 (article 20 [2])

See also

- → Network dynamics
- Sequential dynamical system
- Kathleen Carley
- Network science
- INSNA

External links

- Radcliffe Exploratory Seminar on Dynamic Networks [3]
- Center for Computational Analysis of Social and Organizational Systems (CASOS) [4]

References

[1] http://www.sciencedirect.com/science/journal/01679236
[2] http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6V8S-4KGG5P7-1&_user=4422&_coverDate=08%2F31%2F2007&_rdoc=20&_fmt=high&_orig=browse&_srch=doc-info(%23toc%235878%232007%23999569995%23665759%23FLA%23display%23Volume)&_cdi=5878&_sort=d&_docanchor=&_ct=52&_acct=C000059600&_version=1&_urlVersion=0&_userid=4422&md5=9459e84d7a8863039c7abd5065266250
[3] http://www.eecs.harvard.edu/%7Eparkes/RadcliffeSeminar.htm
[4] http://www.casos.cs.cmu.edu/

Theoretical biology

Theoretical biology is a field of academic study and research that involves the use of models and theories in biology.

Many separate areas of biology fall under the concept of theoretical biology, according to the way they are studied. Some of these areas include: animal behaviour (ethology), biomechanics, biorhythms, cell biology, complexity of biological systems, ecology, enzyme kinetics, evolutionary biology, genetics, immunology, membrane transport, microbiology, molecular structures, morphogenesis, physiological mechanisms, → systems biology and the origin of life. Neurobiology is an example of a subdiscipline of biology which already has a theoretical version of its own, theoretical or computational neuroscience.

The ultimate goal of the theoretical biologist is to explain the biological world using mainly mathematical and computational tools. Though it is ultimately based on observations and experimental results, the theoretical biologist's product is a model or theory, and it is this that chiefly distinguishes the theoretical biologist from other biologists.

Theoretical biologists

- Pere Alberch
- Anthony F. Bartholomay
- Ludwig von Bertalanffy
- J. T. Bonner
- Jack Cowan
- Francis Crick
- Gerd B. Müller
- Walter M. Elsasser
- Claus Emmeche
- Andree Ehresmann
- Marc Feldman
- Ronald A. Fisher
- Brian Goodwin
- Bryan Grenfell
- J. B. S. Haldane
- William D. Hamilton
- Lionel G. Harrison
- Michael Hassell
- Sven Erik Jørgensen
- George Karreman
- Stuart Kauffman
- Kalevi Kull
- Herbert D. Landahl
- Richard Lewontin
- Humberto Maturana
- Robert May
- John Maynard Smith
- James D. Murray
- Howard Pattee

- George R. Price
- Erik Rauch
- Nicolas Rashevsky
- Ronald Brown (mathematician)
- Johannes Reinke
- Robert Rosen
- Peter Schuster
- Rene Thom
- D'Arcy Thompson
- Jakob von Uexküll
- Robert Ulanowicz
- Francisco Varela
- C. H. Waddington
- Arthur Winfree
- Lewis Wolpert
- Sewall Wright
- Christopher Zeeman

See also

- Journal of Theoretical Biology
- Bioinformatics
- Biosemiotics
- → Mathematical biology
- Theoretical ecology
- Artificial life

Bibliographical references

- Bonner, J. T. 1988. *The Evolution of Complexity by Means of Natural Selection*. Princeton: Princeton University Press.
- Hertel, H. 1963. *Structure, Form, Movement*. New York: Reinhold Publishing Corp.
- Mangel, M. 1990. *Special Issue, Classics of Theoretical Biology* (part 1). Bull. Math. Biol. 52(1/2): 1-318.
- Mangel, M. 2006. *The Theoretical Biologist's Toolbox. Quantitative Methods for Ecology and Evolutionary Biology*. Cambridge University Press.
- Prusinkiewicz, P. & Lindenmeyer, A. 1990. *The Algorithmic Beauty of Plants*. Berlin: Springer-Verlag.
- Reinke, J. 1901. *Einleitung in die theoretische Biologie*. Berlin: Verlag von Gebrüder Paetel.
- Thompson, D.W. 1942. *On Growth and Form*. 2nd ed. Cambridge: Cambridge University Press: 2. vols.
- Uexküll, J.v. 1920. *Theoretische Biologie*. Berlin: Gebr. Paetel.
- Vogel, S. 1988. *Life's Devices: The Physical World of Animals and Plants*. Princeton: Princeton University Press.
- Waddington, C.H. 1968-1972. *Towards a Theoretical Biology*. 4 vols. Edinburg: Edinburg University Press.

External links

- Theory of Biological Anthropology (Documents No. 9 and 10 in English) [1]
- Drawing the Line Between Theoretical and Basic Biology (a forum article by Isidro T. Savillo) [2]

Related Journals

- Acta Biotheoretica [3]
- Bioinformatics [4]
- Biological Theory [5]
- BioSystems [6]
- Bulletin of Mathematical Biology [7]
- Ecological Modelling [8]
- Journal of Mathematical Biology [9]
- Journal of Theoretical Biology [10]
- Journal of the Royal Society Interface [11]
- Mathematical Biosciences [12]
- Medical Hypotheses [13]
- Rivista di Biologia-Biology Forum [14]
- Theoretical and Applied Genetics [15]
- Theoretical Biology and Medical Modelling [16]
- Theoretical Population Biology [17]
- Theory in Biosciences [18] (formerly: Biologisches Zentralblatt)

Related societies

- American Mathematical Society [19]
- British Society of Developmental Biology [20]
- European Mathematical Society [21]
- ESMTB: European Society for Mathematical and Theoretical Biology [22]
- The International Biometric Society [23]
- International Society for Ecological Modelling [24]
- The Israeli Society for Theoretical and Mathematical Biology [25]
- London Mathematical Society [26]
- Société Francophone de Biologie Théorique [27]
- Society for Industrial and Applied Mathematics [28]
- Society for Mathematical Biology [29]
- International Society for Biosemiotic Studies [30]

References

[1] http://homepage.uibk.ac.at/~c720126/humanethologie/ws/medicus/block1/inhalt.html
[2] http://www.scientistsolutions.com/t5844-Drawing+the+line+between+Theoretical+and+Basic+Biology.html
[3] http://www.springerlink.com/link.asp?id=102835
[4] http://bioinformatics.oupjournals.org/
[5] http://www.mitpressjournals.org/loi/biot/
[6] http://www.elsevier.com/locate/biosystems
[7] http://www.springerlink.com/content/119979/
[8] http://www.elsevier.com/locate/issn/03043800
[9] http://www.springerlink.com/content/100436/
[10] http://www.elsevier.com/locate/issn/0022-5193
[11] http://publishing.royalsociety.org/index.cfm?page=1058#
[12] http://www.elsevier.com/locate/mbs
[13] http://www.harcourt-international.com/journals/mehy/
[14] http://www.tilgher.it/biologiae.html
[15] http://www.springerlink.com/content/100386/
[16] http://www.tbiomed.com/
[17] http://www.elsevier.com/locate/issn/00405809
[18] http://www.elsevier.com/wps/product/cws_home/701802
[19] http://www.ams.org/
[20] http://www.dundee.ac.uk/lifesciences/BSDB/
[21] http://www.maths.soton.ac.uk/EMIS
[22] http://www.esmtb.org/
[23] http://www.tibs.org/
[24] http://www.isemna.org/
[25] http://bioinformatics.weizmann.ac.il/istmb/
[26] http://www.lms.ac.uk/
[27] http://www.necker.fr/sfbt/
[28] http://www.siam.org/
[29] http://www.smb.org/
[30] http://www.biosemiotics.org/

Mathematical biology

Mathematical biology is also called **theoretical biology**,[1] and sometimes **biomathematics**. It includes at least four major subfields: *biological mathematical modeling*, *relational biology/complex systems biology (CSB)*, *bioinformatics* and *computational biomodeling/biocomputing*. It is an interdisciplinary academic research field with a wide range of applications in biology, medicine[2] and biotechnology.[3]

Mathematical biology aims at the mathematical representation, treatment and modeling of biological processes, using a variety of applied mathematical techniques and tools. It has both theoretical and practical applications in biological, biomedical and biotechnology research. For example, in cell biology, protein interactions are often represented as "cartoon" models, which, although easy to visualize, do not accurately describe the systems studied. In order to do this, precise mathematical models are required. By describing the systems in a quantitative manner, their behavior can be better simulated, and hence properties can be predicted that might not be evident to the experimenter.

Importance

Applying mathematics to biology has a long history, but only recently has there been an explosion of interest in the field. Some reasons for this include:

- the explosion of data-rich information sets, due to the genomics revolution, which are difficult to understand without the use of analytical tools,
- recent development of mathematical tools such as chaos theory to help understand complex, nonlinear mechanisms in biology,
- an increase in computing power which enables calculations and simulations to be performed that were not previously possible, and
- an increasing interest in in silico experimentation due to ethical considerations, risk, unreliability and other complications involved in human and animal research.

For use of basic arithmetics in biology, see relevant topic, such as Serial dilution.

Areas of research

Several areas of specialized research in mathematical and theoretical biology[4] [5] [6] [7] [8] [9] as well as external links to related projects in various universities are concisely presented in the following subsections, including also a large number of appropriate validating references from a list of several thousands of published authors contributing to this field. Many of the included examples are characterised by highly complex, nonlinear, and supercomplex mechanisms, as it is being increasingly recognised that the result of such interactions may only be understood through a combination of mathematical, logical, physical/chemical, molecular and computational models. Due to the wide diversity of specific knowledge involved, biomathematical research is often done in collaboration between mathematicians, biomathematicians, theoretical biologists, physicists, biophysicists, biochemists, bioengineers, engineers, biologists, physiologists, research physicians, biomedical researchers,oncologists, molecular biologists, geneticists, embryologists, zoologists, chemists, etc.

Computer models and automata theory

A monograph on this topic summarizes an extensive amount of published research in this area up to 1987,[10] including subsections in the following areas: computer modeling in biology and medicine, arterial system models, neuron models, biochemical and oscillation networks, quantum automata, [11]quantum computers in molecular biology and genetics, cancer modelling, neural nets, genetic networks, abstract relational biology, metabolic-replication systems, category theory[12] applications in biology and medicine,[13] automata theory,cellular automata, tessallation models[14] [15] and complete self-reproduction [16], chaotic systems in organisms, relational biology and organismic theories.[17] [18] This published report also includes 390 references to peer-reviewed articles by a large number of authors.[19] [20] [21]

Modeling cell and molecular biology

This area has received a boost due to the growing importance of molecular biology.[22]

- Mechanics of biological tissues[23]
- Theoretical enzymology and enzyme kinetics
- Cancer modelling and simulation [24] [25]
- Modelling the movement of interacting cell populations[26]
- Mathematical modelling of scar tissue formation[27]
- Mathematical modelling of intracellular dynamics[28]
- Mathematical modelling of the cell cycle[29]

Modelling physiological systems

- Modelling of arterial disease [30]
- Multi-scale modelling of the heart [31]

Molecular set theory

Molecular set theory was introduced by Anthony Bartholomay, and its applications were developed in mathematical biology and especially in Mathematical Medicine.[32] Molecular set theory (MST) is a mathematical formulation of the wide-sense chemical kinetics of biomolecular reactions in terms of sets of molecules and their chemical transformations represented by set-theoretical mappings between molecular sets. In a more general sense, MST is the theory of molecular categories defined as categories of molecular sets and their chemical transformations represented as set-theoretical mappings of molecular sets. The theory has also contributed to biostatistics and the formulation of clinical biochemistry problems in mathematical formulations of pathological, biochemical changes of interest to Physiology, Clinical Biochemistry and Medicine.[33] [34]

Population dynamics

Population dynamics has traditionally been the dominant field of mathematical biology. Work in this area dates back to the 19th century. The Lotka–Volterra predator-prey equations are a famous example. In the past 30 years, population dynamics has been complemented by evolutionary game theory, developed first by John Maynard Smith. Under these dynamics, evolutionary biology concepts may take a deterministic mathematical form. Population dynamics overlap with another active area of research in mathematical biology: mathematical epidemiology, the study of infectious disease affecting populations. Various models of viral spread have been proposed and analyzed, and provide important results that

may be applied to health policy decisions.

Mathematical methods

A model of a biological system is converted into a system of equations, although the word 'model' is often used synonymously with the system of corresponding equations. The solution of the equations, by either analytical or numerical means, describes how the biological system behaves either over time or at equilibrium. There are many different types of equations and the type of behavior that can occur is dependent on both the model and the equations used. The model often makes assumptions about the system. The equations may also make assumptions about the nature of what may occur.

Mathematical biophysics

The earlier stages of mathematical biology were dominated by mathematical biophysics, described as the application of mathematics in biophysics, often involving specific physical/mathematical models of biosystems and their components or compartments.

The following is a list of mathematical descriptions and their assumptions.

Deterministic processes (dynamical systems)

A fixed mapping between an initial state and a final state. Starting from an initial condition and moving forward in time, a deterministic process will always generate the same trajectory and no two trajectories cross in state space.

- Difference equations – discrete time, continuous state space.
- Ordinary differential equations – continuous time, continuous state space, no spatial derivatives. *See also:* Numerical ordinary differential equations.
- Partial differential equations – continuous time, continuous state space, spatial derivatives. *See also:* Numerical partial differential equations.
- Maps – discrete time, continuous state space.

Stochastic processes (random dynamical systems)

A random mapping between an initial state and a final state, making the state of the system a random variable with a corresponding probability distribution.

- Non-Markovian processes – generalized master equation – continuous time with memory of past events, discrete state space, waiting times of events (or transitions between states) discretely occur and have a generalized probability distribution.
- Jump Markov process – master equation – continuous time with no memory of past events, discrete state space, waiting times between events discretely occur and are exponentially distributed. *See also:* → Monte Carlo method for numerical simulation methods, specifically continuous-time Monte Carlo which is also called kinetic Monte Carlo or the stochastic simulation algorithm.
- Continuous Markov process – stochastic differential equations or a Fokker-Planck equation – continuous time, continuous state space, events occur continuously according to a random Wiener process.

Spatial modelling

One classic work in this area is Alan Turing's paper on morphogenesis entitled *The Chemical Basis of Morphogenesis*, published in 1952 in the Philosophical Transactions of the Royal Society.

- Travelling waves in a wound-healing assay[35]

- Swarming behaviour[36]
- A mechanochemical theory of morphogenesis[37]
- Biological pattern formation[38]
- Spatial distribution modeling using plot samples[39]

Phylogenetics

Phylogenetics is an area of mathematical biology that deals with the reconstruction and analysis of phylogenetic (evolutionary) trees and networks based on inherited characteristics. The main mathematical concepts are trees, X-trees and maximum parsimony trees.

Model example: the cell cycle

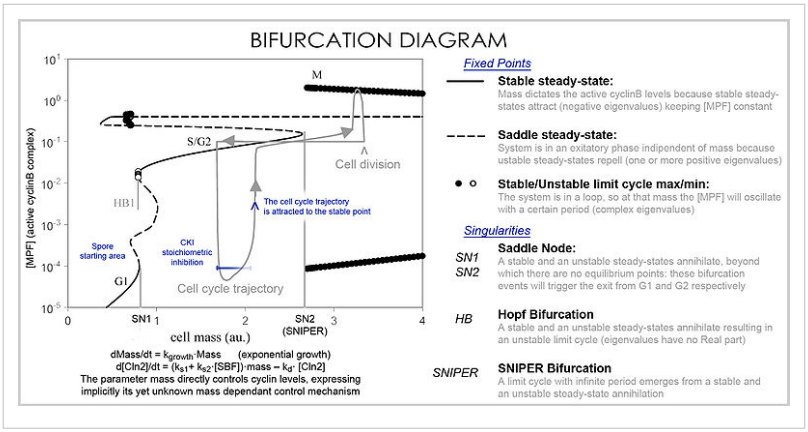
The eukaryotic cell cycle is very complex and is one of the most studied topics, since its misregulation leads to cancers. It is possibly a good example of a mathematical model as it deals with simple calculus but gives valid results. Two research groups [40] [41] have produced several models of the cell cycle simulating several organisms. They have recently produced a generic eukaryotic cell cycle model which can represent a particular eukaryote depending on the values of the parameters, demonstrating that the idiosyncrasies of the individual cell cycles are due to different protein concentrations and affinities, while the underlying mechanisms are conserved (Csikasz-Nagy et al., 2006).

By means of a system of ordinary differential equations these models show the change in time (dynamical system) of the protein inside a single typical cell; this type of model is called a deterministic process (whereas a model describing a statistical distribution of protein concentrations in a population of cells is called a stochastic process).

To obtain these equations an iterative series of steps must be done: first the several models and observations are combined to form a consensus diagram and the appropriate kinetic laws are chosen to write the differential equations, such as rate kinetics for stoichiometric reactions, Michaelis-Menten kinetics for enzyme substrate reactions and Goldbeter–Koshland kinetics for ultrasensitive transcription factors, afterwards the parameters of the equations (rate constants, enzyme efficiency coefficients and Michealis constants) must be fitted to match observations; when they cannot be fitted the kinetic equation is revised and when that is not possible the wiring diagram is modified. The parameters are fitted and validated using observations of both wild type and mutants, such as protein half-life and cell size.

In order to fit the parameters the differential equations need to be studied. This can be done either by simulation or by analysis.

In a simulation, given a starting vector (list of the values of the variables), the progression of the system is calculated by solving the equations at each time-frame in small increments.



In analysis, the proprieties of the equations are used to investigate the behavior of the system depending of the values of the parameters and variables. A system of differential equations can be represented as a vector field, where each vector described the change (in concentration of two or more protein) determining where and how fast the trajectory (simulation) is heading. Vector fields can have several special points: a stable point, called a sink, that attracts in all directions (forcing the concentrations to be at a certain value), an unstable point, either a source or a saddle point which repels (forcing the concentrations to change away from a certain value), and a limit cycle, a closed trajectory towards which several trajectories spiral towards (making the concentrations oscillate).

A better representation which can handle the large number of variables and parameters is called a bifurcation diagram(Bifurcation theory): the presence of these special steady-state points at certain values of a parameter (e.g. mass) is represented by a point and once the parameter passes a certain value, a qualitative change occurs, called a bifurcation, in which the nature of the space changes, with profound consequences for the protein concentrations: the cell cycle has phases (partially corresponding to G1 and G2) in which mass, via a stable point, controls cyclin levels, and phases (S and M phases) in which the concentrations change independently, but once the phase has changed at a bifurcation event (Cell cycle checkpoint), the system cannot go back to the previous levels since at the current mass the vector field is profoundly different and the mass cannot be reversed back through the bifurcation event, making a checkpoint irreversible. In particular the S and M checkpoints are regulated by means of special bifurcations called a Hopf bifurcation and an infinite period bifurcation.

Mathematical/theoretical biologists

- Pere Alberch
- Anthony F. Bartholomay
- J. T. Bonner
- Jack Cowan
- Gerd B. Müller
- Walter M. Elsasser
- Claus Emmeche
- Andree Ehresmann
- Marc Feldman
- Ronald A. Fisher
- Brian Goodwin
- Bryan Grenfell
- J. B. S. Haldane

- William D. Hamilton
- Lionel G. Harrison
- Michael Hassell
- Sven Erik Jørgensen
- George Karreman
- Stuart Kauffman
- Kalevi Kull
- Herbert D. Landahl
- Richard Lewontin
- Humberto Maturana
- Robert May
- John Maynard Smith
- Howard Pattee
- George R. Price
- Erik Rauch
- Nicolas Rashevsky
- Ronald Brown (mathematician)
- Johannes Reinke
- Robert Rosen
- Rene Thom
- Jakob von Uexküll
- Robert Ulanowicz
- Francisco Varela
- C. H. Waddington
- Arthur Winfree
- Lewis Wolpert
- Sewall Wright
- Christopher Zeeman

Mathematical, theoretical and computational biophysicists

- Nicolas Rashevsky
- Ludwig von Bertalanffy
- Francis Crick
- Manfred Eigen
- Walter Elsasser
- Herbert Frohlich, FRS
- Francois Jacob
- Martin Karplus
- George Karreman
- Herbert D. Landahl
- Ilya, Viscount Prigogine
- SirJohn Randall
- James D. Murray
- Bernard Pullman
- Alberte Pullman
- Erwin Schrodinger
- Klaus Schulten

- Peter Schuster
- Zeno Simon
- D'Arcy Thompson
- Murray Gell-Mann

See also

- Abstract relational biology [42][43] [44]
- Biocybernetics
- Bioinformatics
- Biologically-inspired computing
- Biostatistics
- Cellular automata[45]
- Coalescent theory
- → Complex systems biology[46] [47] [48]
- Computational biology
- Dynamical systems in biology[49] [50] [51] [52] [53] [54]
- Epidemiology
- Evolution theories and Population Genetics
  - Population genetics models
  - Molecular evolution theories
- Ewens's sampling formula
- Excitable medium
- → Mathematical models
  - → Molecular modelling
  - Software for molecular modeling
  - Metabolic-replication systems [55][56]
  - Models of Growth and Form
  - Neighbour-sensing model
- Morphometrics
- Organismic systems (OS) [57][58]
- Organismic supercategories [59][60] [61]
- Population dynamics of fisheries
- Protein folding, also blue Gene and folding@home
- Quantum computers
- Quantum genetics
- Relational biology [62]
- Self-reproduction[63] (also called self-replication in a more general context).
- Computational gene models
- → Systems biology[64]
- → Theoretical biology[65]
- Topological models of morphogenesis
  - DNA topology
  - DNA sequencing theory

    For use of basic arithmetics in biology, see relevant topic, such as Serial dilution.
- Biographies
  - Charles Darwin

- D'Arcy Thompson
- Joseph Fourier
- Charles S. Peskin
- Nicolas Rashevsky [66]
- Robert Rosen
- Rosalind Franklin
- Francis Crick
- René Thom
- Vito Volterra

References

- Nicolas Rashevsky. (1938)., *Mathematical Biophysics*. Chicago: University of Chicago Press.
- Robert Rosen, Dynamical system theory in biology. New York, Wiley-Interscience (1970) ISBN 0471735507 [67]
- Israel, G., 2005, "Book on mathematical biology" in Grattan-Guinness, I., ed., *Landmark Writings in Western Mathematics*. Elsevier: 936-44.
- Israel, G (1988), "On the contribution of Volterra and Lotka to the development of modern biomathematics. [68]", *History and philosophy of the life sciences* **10** (1): 37-49, PMID:3045853, http://www.ncbi.nlm.nih.gov/pubmed/3045853
- Scudo, F M (1971), "Vito Volterra and theoretical ecology. [69]", *Theoretical population biology* **2** (1): 1-23, 1971 Mar, PMID:4950157, http://www.ncbi.nlm.nih.gov/pubmed/4950157
- S.H. Strogatz, *Nonlinear dynamics and Chaos: Applications to Physics, Biology, Chemistry, and Engineering*. Perseus, 2001, ISBN 0-7382-0453-6
- N.G. van Kampen, *Stochastic Processes in Physics and Chemistry*, North Holland., 3rd ed. 2001, ISBN 0-444-89349-0
- I. C. Baianu., Computer Models and Automata Theory in Biology and Medicine., *Monograph*, Ch.11 in M. Witten (Editor), *Mathematical Models in Medicine*, vol. **7**., Vol. **7**: 1513-1577 (1987),Pergamon Press:New York, (updated by Hsiao Chen Lin in 2004[70] ,[71] ,[72] ISBN 0080363776 [73] .
- P.G. Drazin, *Nonlinear systems*. C.U.P., 1992. ISBN 0-521-40668-4
- L. Edelstein-Keshet, *Mathematical Models in Biology*. SIAM, 2004. ISBN 0-07-554950-6
- G. Forgacs and S. A. Newman, *Biological Physics of the Developing Embryo*. C.U.P., 2005. ISBN 0-521-78337-2
- A. Goldbeter, *Biochemical oscillations and cellular rhythms*. C.U.P., 1996. ISBN 0-521-59946-6
- L.G. Harrison, *Kinetic theory of living pattern*. C.U.P., 1993. ISBN 0-521-30691-4
- F. Hoppensteadt, *Mathematical theories of populations: demographics, genetics and epidemics*. SIAM, Philadelphia, 1975 (reprinted 1993). ISBN 0-89871-017-0
- D.W. Jordan and P. Smith, *Nonlinear ordinary differential equations*, 2nd ed. O.U.P., 1987. ISBN 0-19-856562-3
- J.D. Murray, *Mathematical Biology*. Springer-Verlag, 3rd ed. in 2 vols.: *Mathematical Biology: I. An Introduction*, 2002 ISBN 0-387-95223-3; *Mathematical Biology: II. Spatial Models and Biomedical Applications*, 2003 ISBN 0-387-95228-4.
- E. Renshaw, *Modelling biological populations in space and time*. C.U.P., 1991. ISBN 0-521-44855-7

- S.I. Rubinow, *Introduction to mathematical biology*. John Wiley, 1975. ISBN 0-471-74446-8
- L.A. Segel, *Modeling dynamic phenomena in molecular and cellular biology*. C.U.P., 1984. ISBN 0-521-27477-X
- L. Preziosi, *Cancer Modelling and Simulation*. Chapman Hall/CRC Press, 2003. ISBN 1-58488-361-8.

Lists of references

- A general list of Theoretical biology/Mathematical biology references, including an updated list of actively contributing authors[74] .
- A list of references for applications of category theory in relational biology[75] .
- An updated list of publications of theoretical biologist Robert Rosen[76]

External

- F. Hoppensteadt, *Getting Started in Mathematical Biology* [77]. Notices of American Mathematical Society, Sept. 1995.
- M. C. Reed, *Why Is Mathematical Biology So Hard?* [78] Notices of American Mathematical Society, March, 2004.
- R. M. May, *Uses and Abuses of Mathematics in Biology* [79]. Science, February 6, 2004.
- J. D. Murray, *How the leopard gets its spots?* [80] Scientific American, 258(3): 80-87, 1988.
- S. Schnell, R. Grima, P. K. Maini, *Multiscale Modeling in Biology* [81], American Scientist, Vol 95, pages 134-142, March-April 2007.
- Chen KC et al. Integrative analysis of cell cycle control in budding yeast. Mol Biol Cell. 2004 Aug;15(8):3841-62.
- Csikász-Nagy A et al. Analysis of a generic model of eukaryotic cell-cycle regulation. Biophys J. 2006 Jun 15;90(12):4361-79.
- Fuss H, et al. Mathematical models of cell cycle regulation. Brief Bioinform. 2005 Jun;6(2):163-77.
- Lovrics A et al. *Time scale and dimension analysis of a budding yeast cell cycle model.* [82] BMC Bioinform. 2006 Nov 9;7:494.

Notes: Inline and online

[1] Mathematical Biology and Theoretical Biophysics-An Outline: What is Life? http://planetmath.org/?op=getobj&from=objects&id=10921
[2] http://www.kli.ac.at/theorylab/EditedVol/W/WittenM1987a.html
[3] http://en.scientificcommons.org/1857372
[4] http://www.kli.ac.at/theorylab/index.html
[5] http://www.springerlink.com/content/w2733h7280521632/
[6] http://en.scientificcommons.org/1857371
[7] http://cogprints.org/3687/
[8] "Research in Mathematical Biology" (http://www.maths.gla.ac.uk/research/groups/biology/kal.htm). Maths.gla.ac.uk. . Retrieved on 2008-09-10.
[9] http://acube.org/volume_23/v23-1p11-36.pdf J. R. Junck. Ten Equations that Changed Biology: Mathematics in Problem-Solving Biology Curricula, *Bioscene*, (1997), 1-36
[10] http://en.scientificcommons.org/1857371
[11] http://planetphysics.org/encyclopedia/QuantumAutomaton.html
[12] http://planetphysics.org/encyclopedia/BibliographyForCategoryTheoryAndAlgebraicTopologyApplicationsInTheoreticalPhysics.html

[13] http://planetphysics.org/encyclopedia/BibliographyForMathematicalBiophysicsAndMathematicalMedicine.html
[14] *Modern Cellular Automata* by Kendall Preston and M. J. B. Duff http://books.google.co.uk/books?id=l0_0q_e-u_UC&dq=cellular+automata+and+tessalation&pg=PP1&ots=ciXYCF3AYm&source=citation&sig=CtaUDhisM7MalS7rZfXvp689y-8&hl=en&sa=X&oi=book_result&resnum=12&ct=result
[15] http://mathworld.wolfram.com/DualTessellation.html
[16] http://planetphysics.org/encyclopedia/ETACAxioms.html
[17] Baianu, I. C. 1987, Computer Models and Automata Theory in Biology and Medicine., in M. Witten (ed.),*Mathematical Models in Medicine*, vol. **7**., Ch.11 Pergamon Press, New York, 1513-1577. http://cogprints.org/3687/
[18] http://www.kli.ac.at/theorylab/EditedVol/W/WittenM1987a.html
[19] http://www.springerlink.com/content/w2733h7280521632/
[20] Currently available for download as an updated PDF: http://cogprints.ecs.soton.ac.uk/archive/00003718/01/COMPUTER_SIMULATIONCOMPUTABILITYBIOSYSTEMSrefnew.pdf
[21] http://planetphysics.org/encyclopedia/BibliographyForMathematicalBiophysics.html
[22] "Research in Mathematical Biology" (http://www.maths.gla.ac.uk/research/groups/biology/kal.htm). Maths.gla.ac.uk. . Retrieved on 2008-09-10.
[23] http://www.maths.gla.ac.uk/~rwo/research_areas.htm
[24] http://www.springerlink.com/content/71958358k273622q/
[25] http://calvino.polito.it/~mcrtn/
[26] http://www.ma.hw.ac.uk/~jas/researchinterests/index.html
[27] http://www.ma.hw.ac.uk/~jas/researchinterests/scartissueformation.html
[28] http://www.sbi.uni-rostock.de/dokumente/p_gilles_paper.pdf
[29] http://mpf.biol.vt.edu/Research.html
[30] http://www.maths.gla.ac.uk/~nah/research_interests.html
[31] http://www.integrativebiology.ox.ac.uk/heartmodel.html
[32] http://planetphysics.org/encyclopedia/CategoryOfMolecularSets2.html
[33] Representation of Uni-molecular and Multimolecular Biochemical Reactions in terms of Molecular Set Transformations http://planetmath.org/?op=getobj&from=objects&id=10770
[34] http://planetphysics.org/encyclopedia/CategoryOfMolecularSets2.html
[35] http://www.maths.ox.ac.uk/~maini/public/gallery/twwha.htm
[36] http://www.math.ubc.ca/people/faculty/keshet/research.html
[37] http://www.maths.ox.ac.uk/~maini/public/gallery/mctom.htm
[38] http://www.maths.ox.ac.uk/~maini/public/gallery/bpf.htm
[39] http://links.jstor.org/sici?sici=0030-1299%28199008%2958%3A3%3C257%3ASDOTMU%3E2.0.CO%3B2-S&size=LARGE&origin=JSTOR-enlargePage
[40] "The JJ Tyson Lab" (http://mpf.biol.vt.edu/Tyson Lab.html). Virginia Tech. . Retrieved on 2008-09-10.
[41] "The Molecular Network Dynamics Research Group" (http://cellcycle.mkt.bme.hu/). Budapest University of Technology and Economics. .
[42] http://www.kli.ac.at/theorylab/ALists/Authors_R.html
[43] http://planetphysics.org/encyclopedia/AbstractRelationalBiologyARB.html
[44] http://www.kli.ac.at/theorylab/EditedVol/M/MatsunoKDose_84.html
[45] Baianu, I. C. 1987, Computer Models and Automata Theory in Biology and Medicine., in M. Witten (ed.),*Mathematical Models in Medicine*, vol. **7**., Ch.11 Pergamon Press, New York, 1513-1577. http://www.springerlink.com/content/w2733h7280521632/
[46] http://www.springerlink.com/content/v1rt05876h74v607/?p=2bd3993c33644512ba7069ed7fad0046&pi=1
[47] http://www.springerlink.com/content/j7t56r530140r88p/?p=2bd3993c33644512ba7069ed7fad0046&pi=3
[48] http://www.springerlink.com/content/98303486x3l07jx3/
[49] Robert Rosen, *Dynamical system theory in biology.* New York, Wiley-Interscience (1970) ISBN 0471735507 http://www.worldcat.org/oclc/101642
[50] http://www.springerlink.com/content/j7t56r530140r88p/?p=2bd3993c33644512ba7069ed7fad0046&pi=3
[51] http://cogprints.org/3674/
[52] http://cogprints.org/3829/
[53] http://www.ncbi.nlm.nih.gov/pubmed/4327361
[54] http://www.springerlink.com/content/98303486x3l07jx3/
[55] http://planetphysics.org/encyclopedia/RSystemsCategoryOfM.html
[56] http://www.kli.ac.at/theorylab/ALists/Authors_R.html
[57] http://planetphysics.org/encyclopedia/OrganismicSetTheory.html

[58] Organisms as Super-complex Systems http://planetmath.org/?op=getobj&from=objects&id=10890
[59] http://planetphysics.org/encyclopedia/OrganismicSetTheory.html
[60] http://www.springerlink.com/content/98303486x3l07jx3/
[61] http://planetmath.org/encyclopedia/SupercategoriesOfComplexSystems.html
[62] http://planetmath.org/?op=getobj&from=objects&id=10921
[63] http://planetmath.org/?method=l2h&from=objects&name=NaturalTransformationsOfOrganismicStructures&op=getobj
[64] http://www.kli.ac.at/theorylab/ALists/Authors_R.html
[65] http://www.kli.ac.at/theorylab/index.html
[66] http://planetphysics.org/encyclopedia/NicolasRashevsky.html
[67] http://www.worldcat.org/oclc/101642
[68] http://www.ncbi.nlm.nih.gov/pubmed/3045853
[69] http://www.ncbi.nlm.nih.gov/pubmed/4950157
[70] http://cogprints.org/3718/1/COMPUTER_SIMULATIONCOMPUTABILITYBIOSYSTEMSrefnew.pdf
[71] http://www.springerlink.com/content/w2733h7280521632/
[72] http://www.springerlink.com/content/n8gw445012267381/
[73] http://www.bookfinder.com/dir/i/Mathematical_Models_in_Medicine/0080363776/
[74] http://www.kli.ac.at/theorylab/index.html
[75] http://planetmath.org/?method=l2h&from=objects&id=10746&op=getobj
[76] Publications list for Robert Rosen http://www.people.vcu.edu/~mikuleck/rosen.htm
[77] http://www.ams.org/notices/199509/hoppensteadt.pdf
[78] http://www.resnet.wm.edu/~jxshix/math490/reed.pdf
[79] http://www.resnet.wm.edu/~jxshix/math490/may.pdf
[80] http://www.resnet.wm.edu/~jxshix/math490/murray.doc
[81] http://eprints.maths.ox.ac.uk/567/01/224.pdf
[82] http://www.biomedcentral.com/content/pdf/1471-2105-7-494.pdf

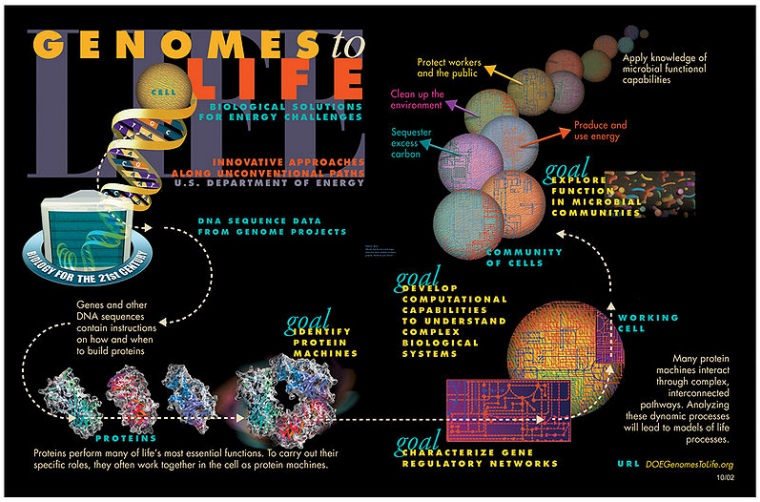
External links

- Theoretical and mathematical biology website (http://www.kli.ac.at/theorylab/index.html)
- Complexity Discussion Group (http://www.complex.vcu.edu/)
- Integrative cancer biology modeling and Complex systems biology (http://fs512.fshn.uiuc.edu/ComplexSystemsBiology.htm)
- UCLA Biocybernetics Laboratory (http://biocyb.cs.ucla.edu/research.html)
- TUCS Computational Biomodelling Laboratory (http://www.tucs.fi/research/labs/combio.php)
- Nagoya University Division of Biomodeling (http://www.agr.nagoya-u.ac.jp/english/e3senko-1.html)
- Technische Universiteit Biomodeling and Informatics (http://www.bmi2.bmt.tue.nl/Biomedinf/)
- BioCybernetics Wiki, a vertical wiki on biomedical cybernetics and systems biology (http://wiki.biological-cybernetics.de)
- Society for Mathematical Biology (http://www.smb.org/)
- Bulletin of Mathematical Biology (http://www.springerlink.com/content/119979/)
- European Society for Mathematical and Theoretical Biology (http://www.esmtb.org/)
- Journal of Mathematical Biology (http://www.springerlink.com/content/100436/)
- Biomathematics Research Centre at University of Canterbury (http://www.math.canterbury.ac.nz/bio/)
- Centre for Mathematical Biology at Oxford University (http://www.maths.ox.ac.uk/cmb/)
- Mathematical Biology at the National Institute for Medical Research (http://mathbio.nimr.mrc.ac.uk/)

- Institute for Medical BioMathematics (http://www.imbm.org/)
- *Mathematical Biology Systems of Differential Equations* (http://eqworld.ipmnet.ru/en/solutions/syspde/spde-toc2.pdf) from EqWorld: The World of Mathematical Equations
- Systems Biology Workbench - a set of tools for modelling biochemical networks (http://sbw.kgi.edu)
- The Collection of Biostatistics Research Archive (http://www.biostatsresearch.com/repository/)
- Statistical Applications in Genetics and Molecular Biology (http://www.bepress.com/sagmb/)
- The International Journal of Biostatistics (http://www.bepress.com/ijb/)

Systems biology

Systems biology is a biology-based inter-disciplinary study field that focuses on the systematic study of complex interactions in biological systems, thus using a new perspective (holism instead of reduction) to study them. Particularly from year 2000 onwards, the term is used widely in the biosciences, and in a variety of contexts. Because the scientific method has been used primarily toward reductionism, one of the goals of systems biology is to discover new emergent properties that may arise from the systemic view used by this discipline in order to understand better the entirety of processes that happen in a biological system.



Example of systems biology research.

Overview

Systems biology can be considered from a number of different aspects:

- Some sources discuss systems biology as a **field of study**, particularly, the study of the interactions between the components of *biological systems*, and how these interactions give rise to the function and behavior of that system (for example, the enzymes and metabolites in a metabolic pathway).[1] [2]
- Other sources consider systems biology as a **paradigm**, usually defined in antithesis to the so-called reductionist paradigm, although fully consistent with the scientific method. The distinction between the two paradigms is referred to in these quotations:

  "*The reductionist approach has successfully identified most of the components and many of the interactions but, unfortunately, offers no convincing concepts or methods to understand how system properties emerge...the pluralism of causes and effects in biological networks is better addressed by observing, through quantitative measures,*

multiple components simultaneously and by rigorous data integration with mathematical models" Science[3]

"*Systems biology...is about putting together rather than taking apart, integration rather than reduction. It requires that we develop ways of thinking about integration that are as rigorous as our reductionist programmes, but different....It means changing our philosophy, in the full sense of the term*" Denis Noble[4]

- Still other sources view systems biology in terms of the **operational protocols used for performing research**, namely a cycle composed of theory, analytic or computational modelling to propose specific testable hypotheses about a biological system, experimental validation, and then using the newly acquired quantitative description of cells or cell processes to refine the computational model or theory.[5] [6] Since the objective is a model of the interactions in a system, the experimental techniques that most suit systems biology are those that are system-wide and attempt to be as complete as possible. Therefore, transcriptomics, metabolomics, proteomics and high-throughput techniques are used to collect quantitative data for the construction and validation of models.
- Engineers consider systems biology as the application of dynamical systems theory to molecular biology.
- Finally, some sources see it as a **socioscientific phenomenon** defined by the strategy of pursuing integration of complex data about the interactions in biological systems from diverse experimental sources using interdisciplinary tools and personnel.

This variety of viewpoints is illustrative of the fact that systems biology refers to a cluster of peripherally overlapping concepts rather than a single well-delineated field. However the term has widespread currency and popularity as of 2007, with chairs and institutes of systems biology proliferating worldwide (Such as the Institute for Systems Biology).

History

Systems biology finds its roots in:

- the quantitative modelling of enzyme kinetics, a discipline that flourished between 1900 and 1970,
- the simulations developed to study neurophysiology, and
- control theory and cybernetics.

One of the theorists who can be seen as a precursor of systems biology is Ludwig von Bertalanffy with his general systems theory. One of the first numerical simulations in biology was published in 1952 by the British neurophysiologists and Nobel prize winners Alan Lloyd Hodgkin and Andrew Fielding Huxley, who constructed a mathematical model that explained the action potential propagating along the axon of a neuronal cell.[7] Their model described a cellular function emerging from the interaction between two different molecular components, a potassium and a sodium channels, and can therefore be seen as the beginning of computational systems biology.[8] In 1960, Denis Noble developed the first computer model of the heart pacemaker.[9]

The formal study of systems biology, as a distinct discipline, was launched by systems theorist Mihajlo Mesarovic in 1966 with an international symposium at the Case Institute of Technology in Cleveland, Ohio entitled "Systems Theory and Biology."[10] [11]

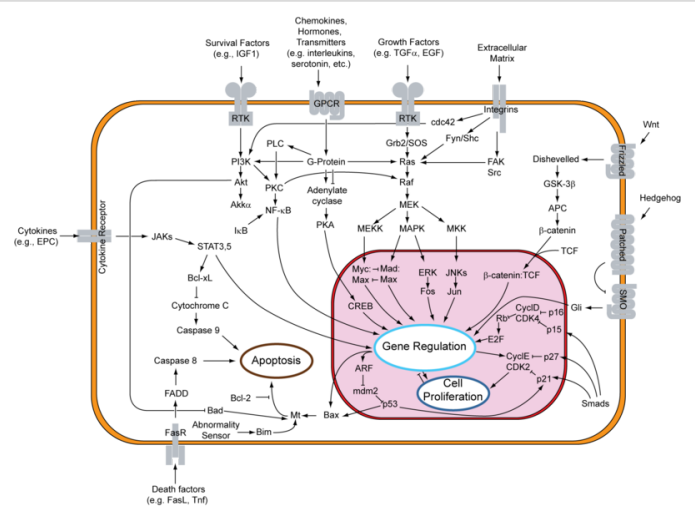
The 1960s and 1970s saw the development of several approaches to study complex molecular systems, such as the Metabolic Control Analysis and the biochemical systems theory. The successes of molecular biology throughout the 1980s, coupled with a skepticism toward → theoretical biology, that then promised more than it achieved, caused the quantitative modelling of biological processes to become a somewhat minor field.

However the birth of functional genomics in the 1990s meant that large quantities of high quality data became available, while the computing power exploded, making more realistic models possible. In 1997, the group of Masaru Tomita published the first quantitative model of the metabolism of a whole (hypothetical) cell.

Around the year 2000, when Institutes of Systems Biology were established in Seattle and Tokyo, systems biology emerged as a movement in its own right, spurred on by the completion of various genome projects, the large increase in data from the omics (e.g. genomics and proteomics) and the accompanying advances in high-throughput experiments and bioinformatics. Since then, various research institutes dedicated to systems biology have been developed. As of summer 2006, due to a shortage of people in systems biology[12] several doctoral training centres in systems biology have been established in many parts of the world.

Techniques associated with systems biology

According to the interpretation of System Biology as the ability to obtain, integrate and analyze complex data from multiple experimental sources using interdisciplinary tools, some typical technology platforms are:



Overview of signal transduction pathways

- Transcriptomics: whole cell or tissue gene expression measurements by DNA microarrays or serial analysis of gene expression
- Proteomics: complete identification of proteins and protein expression patterns of a cell or tissue through two-dimensional gel electrophoresis and mass spectrometry or multi-dimensional protein identification techniques (advanced HPLC systems coupled with mass spectrometry). Sub disciplines include phosphoproteomics, glycoproteomics and other methods to detect chemically modified proteins.
- Metabolomics: identification and measurement of all small-molecules metabolites within a cell or tissue
- Glycomics: identification of the entirety of all carbohydrates in a cell or tissue.

In addition to the identification and quantification of the above given molecules further techniques analyze the dynamics and interactions within a cell. This includes:

- → Interactomics which is used mostly in the context of protein-protein interaction but in theory encompasses interactions between all molecules within a cell,

- Fluxomics, which deals with the dynamic changes of molecules within a cell over time,
- Biomics: systems analysis of the biome.

The investigations are frequently combined with large scale perturbation methods, including gene-based (RNAi, mis-expression of wild type and mutant genes) and chemical approaches using small molecule libraries. Robots and automated sensors enable such large-scale experimentation and data acquisition. These technologies are still emerging and many face problems that the larger the quantity of data produced, the lower the quality. A wide variety of quantitative scientists (computational biologists, statisticians, mathematicians, computer scientists, engineers, and physicists) are working to improve the quality of these approaches and to create, refine, and retest the models to accurately reflect observations.

The investigations of a single level of biological organization (such as those listed above) are usually referred to as Systematic Systems Biology. Other areas of Systems Biology includes Integrative Systems Biology, which seeks to integrate different types of information to advance the understanding the biological whole, and Dynamic Systems Biology, which aims to uncover how the biological whole changes over time (during evolution, for example, the onset of disease or in response to a perturbation). Functional Genomics may also be considered a sub-field of Systems Biology.

The systems biology approach often involves the development of mechanistic models, such as the reconstruction of dynamic systems from the quantitative properties of their elementary building blocks.[13] [14] For instance, a cellular network can be modelled mathematically using methods coming from chemical kinetics and control theory. Due to the large number of parameters, variables and constraints in cellular networks, numerical and computational techniques are often used. Other aspects of computer science and informatics are also used in systems biology. These include new forms of computational model, such as the use of process calculi to model biological processes, the integration of information from the literature, using techniques of information extraction and text mining, the development of online databases and repositories for sharing data and models (such as BioModels Database), approaches to database integration and software interoperability via loose coupling of software, websites and databases[15] and the development of syntactically and semantically sound ways of representing biological models, such as the Systems Biology Markup Language (SBML).

See also

Related fields

- Complex systems biology
- Complex systems
- Complex systems biology
- Bioinformatics
- Biological network inference
- Biological systems engineering
- Biomedical cybernetics
- Biostatistics
- Theoretical Biophysics
- Relational Biology
- Translational Research
- Computational biology
- Computational systems biology
- Scotobiology
- Synthetic biology
- Systems biology modeling
- Systems ecology
- Systems immunology

Related terms

- Life
- Artificial life
- Gene regulatory network
- Metabolic network modelling
- Living systems theory
- Network Theory of Aging
- Regulome
- Systems Biology Markup Language (SBML)
- SBO
- Viable System Model
- Antireductionism

Systems biologists

- Category:Systems biologists

Lists

- Category:Systems biologists
- List of systems biology conferences
- List of omics topics in biology
- List of publications in systems biology
- List of systems biology research groups

References

[1] Snoep J.L. and Westerhoff H.V.; Alberghina L. and Westerhoff H.V. (Eds.) (2005.). "From isolation to integration, a systems biology approach for building the Silicon Cell". *Systems Biology: Definitions and Perspectives*: p7, Springer-Verlag.

[2] "Systems Biology - the 21st Century Science" (http://www.systemsbiology.org/Intro_to_ISB_and_Systems_Biology/Systems_Biology_--_the_21st_Century_Science). .

[3] Sauer, U. et al. (27 April 2007). "Getting Closer to the Whole Picture". *Science* **316**: 550. doi: 10.1126/science.1142502 (http://dx.doi.org/10.1126/science.1142502). PMID 17463274.

[4] Denis Noble (2006). *The Music of Life: Biology beyond the genome*. Oxford University Press. ISBN 978-0199295739. p21

[5] "Systems Biology: Modelling, Simulation and Experimental Validation" (http://www.bbsrc.ac.uk/science/areas/ebs/themes/main_sysbio.html). .

[6] Kholodenko B.N., Bruggeman F.J., Sauro H.M.; Alberghina L. and Westerhoff H.V.(Eds.) (2005.). "Mechanistic and modular approaches to modeling and inference of cellular regulatory networks". *Systems Biology: Definitions and Perspectives*: p143, Springer-Verlag.

[7] Hodgkin AL, Huxley AF (1952). "A quantitative description of membrane current and its application to conduction and excitation in nerve". *J Physiol* **117**: 500–544. PMID 12991237.

[8] Le Novere (2007). "The long journey to a Systems Biology of neuronal function". *BMC Systems Biology* **1**: 28. doi: 10.1186/1752-0509-1-28 (http://dx.doi.org/10.1186/1752-0509-1-28).

[9] Noble D (1960). "Cardiac action and pacemaker potentials based on the Hodgkin-Huxley equations". *Nature* **188**: 495–497. doi: 10.1038/188495b0 (http://dx.doi.org/10.1038/188495b0). PMID 13729365.

[10] Mesarovic, M. D. (1968). *Systems Theory and Biology*. Springer-Verlag.

[11] " A Means Toward a New Holism (http://www.jstor.org/view/00368075/ap004022/00a00220/0)". *Science* **161** (3836): 34-35. doi: 10.1126/science.161.3836.34 (http://dx.doi.org/10.1126/science.161.3836.34). .

[12] "Working the Systems" (http://sciencecareers.sciencemag.org/career_development/previous_issues/articles/2006_03_03/working_the_systems/(parent)/158). .

[13] Gardner, TS; di Bernardo D, Lorenz D and Collins JJ (4 July 2003). "Inferring genetic networks and identifying compound of action via expression profiling". *Science* **301**: 102-1005. doi: 10.1126/science.1081900 (http://dx.doi.org/10.1126/science.1081900). PMID 12843395.

[14] di Bernardo, D; Thompson MJ, Gardner TS, Chobot SE, Eastwood EL, Wojtovich AP, Elliot SJ, Schaus SE and Collins JJ (March 2005). "Chemogenomic profiling on a genome-wide scale using reverse-engineered gene

networks". *Nature Biotechnology* **23**: 377-383. doi: 10.1038/nbt1075 (http://dx.doi.org/10.1038/nbt1075). PMID 15765094.

[15] such as Gaggle (http://gaggle.systemsbiology.net), SBW (http://sys-bio.org)), or commercial suits, e.g., MetaCore (http://www.genego.com/metacore.php) and MetaDrug (http://www.genego.com/metadrug.php)

Further reading

Books

- Hiroaki Kitano (editor). *Foundations of Systems Biology.* MIT Press: 2001. ISBN 0-262-11266-3
- CP Fall, E Marland, J Wagner and JJ Tyson (Editors). "Computational Cell Biology." Springer Verlag: 2002 ISBN 0-387-95369-8
- G Bock and JA Goode (eds).*In Silico*" *Simulation of Biological Processes*, Novartis Foundation Symposium 247. John Wiley & Sons: 2002. ISBN 0-470-84480-9
- E Klipp, R Herwig, A Kowald, C Wierling, and H Lehrach. *Systems Biology in Practice.* Wiley-VCH: 2005. ISBN 3-527-31078-9
- L. Alberghina and H. Westerhoff (Editors) – *Systems Biology: Definitions and Perspectives*, Topics in Current Genetics 13, Springer Verlag (2005), ISBN 978-3540229681
- A Kriete, R Eils. *Computational Systems Biology.*, Elsevier - Academic Press: 2005. ISBN 0-12-088786-X
- K. Sneppen and G. Zocchi, (2005) *Physics in Molecular Biology*, Cambridge University Press, ISBN 0-521-84419-3
- D. Noble, *The Music of life. Biology beyond the genome* Oxford University Press (http://www.musicoflife.co.uk/) 2006. ISBN 0199295735, ISBN 978-0199295739
- Z. Szallasi, J. Stelling, and V.Periwal (eds.) System Modeling in Cellular Biology: From Concepts to Nuts and Bolts (Hardcover), MIT Press: 2006, ISBN 0-262-19548-8
- B Palsson, *Systems Biology - Properties of Reconstructed Networks.* Cambridge University Press: 2006. (http://gcrg.ucsd.edu/book/index.html) ISBN 978-0-521-85903-5
- K Kaneko. *Life: An Introduction to Complex Systems Biology.* Springer: 2006. ISBN 3540326669
- U Alon. *An Introduction to Systems Biology: Design Principles of Biological Circuits.* CRC Press: 2006. ISBN 1-58488-642-0 - emphasis on Network Biology (For a comparative review of Alon, Kaneko and Palsson see Werner, E. (March 29, 2007). " All systems go (http://www.nature.com/nature/journal/v446/n7135/pdf/446493a.pdf)" (PDF). *Nature* **446**: 493-494. doi: 10.1038/446493a (http://dx.doi.org/10.1038/446493a). http://www.nature.com/nature/journal/v446/n7135/pdf/446493a.pdf.)
- Andriani Daskalaki (editor) "Handbook of Research on Systems Biology Applications in Medicine" Medical Information Science Reference, October 2008 ISBN 978-1-60566-076-9

Journals

- BMC Systems Biology (http://www.biomedcentral.com/bmcsystbiol) - open access journal on systems biology
- Molecular Systems Biology (http://www.nature.com/msb) - open access journal on systems biology
- IET Systems Biology (http://www.ietdl.org/IET-SYB) - not open access journal on systems biology

Articles

- Binnewies, Tim Terence, Miller, WG, Wang, G. *The complete genome sequence and analysis of the human pathogen Campylobacter lari* (http://www.bio.dtu.dk/English/Publications/1/all.aspx?lg=showcommon&id=231324). Published in journal: Foodborne Pathog Disease (ISSN 1535-3141) , vol: 5, issue: 4, pages: 371-386, 2008, Mary Ann Liebert, Inc. Publishers.
- M. Tomita, Hashimoto K, Takahashi K, Shimizu T, Matsuzaki Y, Miyoshi F, Saito K, Tanida S, Yugi K, Venter JC, Hutchison CA. E-CELL: Software Environment for Whole Cell Simulation. Genome Inform Ser Workshop Genome Inform. 1997;8:147-155. (http://web.sfc.keio.ac.jp/~mt/mt-lab/publications/Paper/ecell/bioinfo99/btc007_gml.html)
- ScienceMag.org (http://www.sciencemag.org/content/vol295/issue5560/) - Special Issue: Systems Biology, *Science*, Vol 295, No 5560, March 1, 2002
- Marc Vidal and Eileen E. M. Furlong. Nature Reviews Genetics 2004 From OMICS to systems biology (http://www.nature.com/nrg/journal/v5/n10/poster/omics/index.html)
- Marc Facciotti, Richard Bonneau, Leroy Hood and Nitin Baliga. Current Genomics 2004 Systems Biology Experimental Design - Considerations for Building Predictive Gene Regulatory Network Models for Prokaryotic Systems (http://www.ingentaconnect.com/content/ben/cg/2004/00000005/00000007/art00002)
- Katia Basso, Adam A Margolin, Gustavo Stolovitzky, Ulf Klein, Riccardo Dalla-Favera, Andrea Califano, (2005) "Reverse engineering of regulatory networks in human B cells" (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15778709&query_hl=7). Nat Genet;37(4):382-90
- Mario Jardon Systems Biology: An Overview (http://www.scq.ubc.ca/?p=253) - a review from the Science Creative Quarterly, 2005
- Johnjoe McFadden, Guardian.co.uk (http://www.guardian.co.uk/life/science/story/0,12996,1477776,00.html) - 'The unselfish gene: The new biology is reasserting the primacy of the whole organism - the individual - over the behaviour of isolated genes', *The Guardian* (May 6, 2005)
- Pharoah, M.C. (online). Looking to systems theory for a reductive explanation of phenomenal experience and evolutionary foundations for higher order thought (http://homepage.ntlworld.com/m.pharoah/) Retrieved Jan, 15 2008.
- WTEC Panel Report on International Research and Development in Systems Biology (http://www.wtec.org/sysbio/welcome.htm) (2005)
- E. Werner, "The Future and Limits of Systems Biology", Science STKE (http://stke.sciencemag.org/content/vol2005/issue278/) 2005, pe16 (2005).
- Francis J. Doyle and Jörg Stelling, "Systems interface biology" (http://www.journals.royalsoc.ac.uk/openurl.asp?genre=article&doi=10.1098/rsif.2006.0143) *J. R. Soc. Interface* Vol 3, No 10 2006

- Kahlem, P. and Birney E. (2006). "Dry work in a wet world: computation in systems biology." Mol Syst Biol 2: 40. (http://www.nature.com/doifinder/10.1038/msb4100080)
- E. Werner, "All systems go" (http://www.nature.com/nature/journal/v446/n7135/pdf/446493a.pdf), "Nature" (http://www.nature.com/nature/journal/v446/n7135/index.html) vol 446, pp 493–494, March 29, 2007. (Review of three books (Alon, Kaneko, and Palsson) on systems biology.)
- Santiago Schnell, Ramon Grima, Philip K. Maini, "Multiscale Modeling in Biology" (http://www.americanscientist.org/template/AssetDetail/assetid/54784), American Scientist, Vol 95, pages 134-142, March-April 2007.
- TS Gardner, D di Bernardo, D Lorenz and JJ Collins. "Inferring genetic networks and identifying compound of action via expression profiling." (http://www.bu.edu/abl/publications.html) Science 301: 102-105 (2003).
- Jeffery C. Way and Pamela A. Silver, Why We Need Systems Biology (http://cs.calstatela.edu/wiki/images/9/9b/Silver.pdf)
- H.S. Wiley, "Systems Biology - Beyond the Buzz." The Scientist (http://www.the-scientist.com/2006/6/1/52/1/). June 2006.]
- Nina Flanagan, "Systems Biology Alters Drug Development." (http://www.genengnews.com/articles/chitem.aspx?aid=2337) Genetic Engineering & Biotechnology News, January 2008

External links

- Systems Biology - BioChemWeb.org (http://www.biochemweb.org/systems.shtml)
- Systems Biology Portal (http://www.systems-biology.org/) - administered by the Systems Biology Institute
- Semantic Systems Biology (http://www.semantic-systems-biology.org)
- SystemsX.ch (http://www.systemsx.ch/) - The Swiss Initiative in Systems Biology
- Systems Biology at the Pacific Northwest National Laboratory (http://www.sysbio.org/)

DNA Dynamics

DNA Molecular dynamics modeling involves simulations of DNA molecular geometry and topology changes with time as a result of both intra- and inter- molecular interactions of DNA. Whereas molecular models of Deoxyribonucleic acid (DNA) molecules such as closely packed spheres (CPK models) made of plastic or metal wires for 'skeletal models' are useful representations of static DNA structures, their usefulness is very limited for representing complex DNA dynamics. Computer molecular modeling allows both animations and molecular dynamics simulations that are very important for understanding how DNA functions *in vivo*.

An old standing dynamic problem is how DNA "self-replication" takes place in living cells that should involve transient uncoiling of supercoiled DNA fibers. Although DNA consists of relatively rigid, very large elongated biopolymer molecules called "fibers" or chains its molecular structure *in vivo* undergoes dynamic configuration changes that involve dynamically attached water molecules, ions or proteins/enzymes. Supercoiling, packing with histones in chromosome structures, and other such supramolecular aspects also involve *in vivo* DNA topology which is even more complex than DNA molecular geometry, thus turning molecular modeling of DNA dynamics into a series of challenging problems for biophysical chemists, molecular biologists and biotechnologists. Thus, DNA exists in multiple stable geometries (called conformational isomerism) and has a rather large number of configurational, quantum states which are close to each other in energy on the potential energy surface of the DNA molecule.

Such varying molecular geometries can also be computed, at least in principle, by employing *ab initio* → quantum chemistry methods that can attain high accuracy for small molecules, although claims that acceptable accuracy can be also achieved for polynuclelotides, as well as DNA conformations, were recently made on the basis of VCD spectral data. Such quantum geometries define an important class of *ab initio* molecular models of DNA whose exploration has barely started especially in connection with results obtained by VCD in solutions. More detailed comparisons with such *ab initio* quantum computations are in principle obtainable through 2D-FT NMR spectroscopy and relaxation studies of polynucleotide solutions or specifically labeled DNA, as for example with deuterium labels.

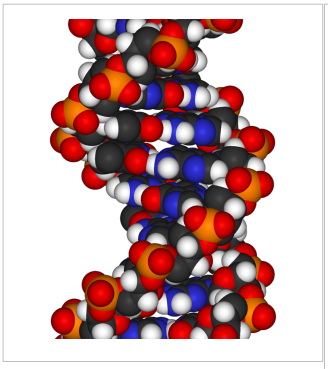
Importance of DNA molecular structure and dynamics modeling for Genomics and beyond

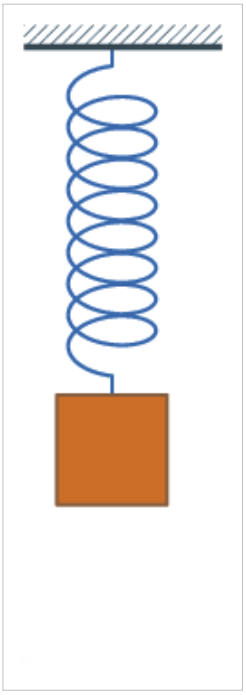
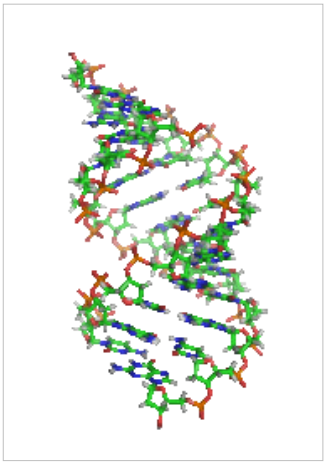
From the very early stages of structural studies of DNA by X-ray diffraction and biochemical means, molecular models such as the Watson-Crick double-helix model were successfully employed to solve the 'puzzle' of DNA structure, and also find how the latter relates to its key functions in living cells. The first high quality X-ray diffraction patterns of A-DNA were reported by Rosalind Franklin and Raymond Gosling in 1953[1] . The first reports of a double-helix molecular model of B-DNA structure were made by Watson and Crick in 1953[2] [3] . Then Maurice F. Wilkins, A. Stokes and H.R. Wilson, reported the first X-ray patterns of *in vivo* B-DNA in partially oriented salmon sperm heads [4] . The development of the first correct double-helix molecular model of DNA by Crick and Watson may not have been possible without the biochemical evidence for the nucleotide base-pairing ([A---T]; [C---G]), or Chargaff's rules[5] [6] [7] [8] [9] [10] . Although such initial

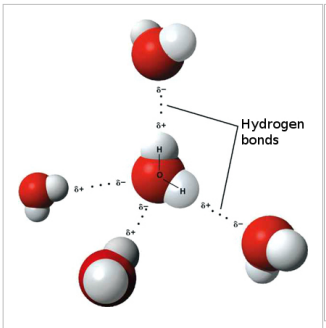
studies of DNA structures with the help of molecular models were essentially static, their consequences for explaining the *in vivo* functions of DNA were significant in the areas of protein biosynthesis and the quasi-universality of the genetic code. Epigenetic transformation studies of DNA *in vivo* were however much slower to develop in spite of their importance for embryology, morphogenesis and cancer research. Such chemical dynamics and biochemical reactions of DNA are much more complex than the molecular dynamics of DNA physical interactions with water, ions and proteins/enzymes in living cells.

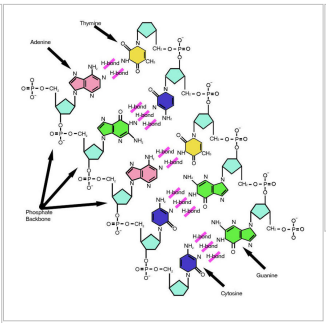
Animated DNA molecular models and hydrogen-bonding

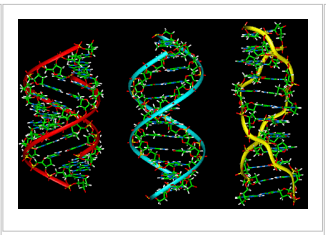
Animated molecular models allow one to visually explore the three-dimensional (3D) structure of DNA. The first DNA model is a space-filling, or CPK, model of the DNA double-helix whereas the third is an animated wire, or skeletal type, molecular model of DNA. The last two DNA molecular models in this series depict quadruplex DNA [11] that may be involved in certain cancers[12] [13] . The first CPK model in the second row is a molecular model of hydrogen bonds between water molecules in ice that are broadly similar to those found in DNA; the hydrogen bonding dynamics and proton exchange is however very different by many orders of magnitude between the two systems of fully hydrated DNA and water molecules in ice. Thus, the DNA dynamics is complex, involving nanosecond and several tens of picosecond time scales, whereas that of liquid ice is on the picosecond time scale, and that of proton exchange in ice is on the millisecond time scale; the proton exchange rates in DNA and attached proteins may vary from picosecond to nanosecond, minutes or years, depending on the exact locations of the exchanged protons in the large biopolymers. The simple harmonic oscillator 'vibration' in the third, animated image of the next gallery is only an oversimplified dynamic representation of the longitudinal vibrations of the DNA intertwined helices which were found to be anharmonic rather than harmonic as often assumed in quantum dynamic simulations of DNA.

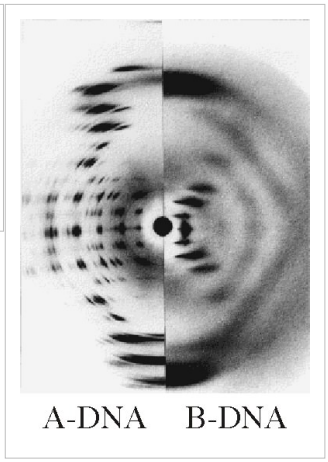


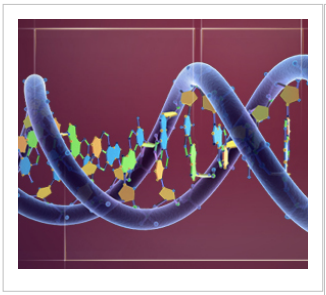



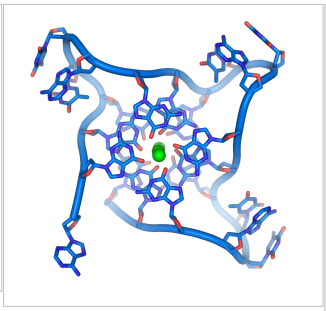


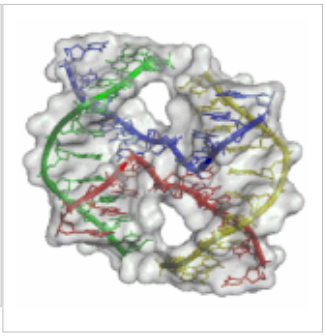










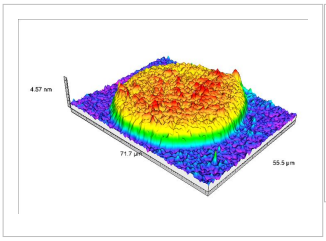


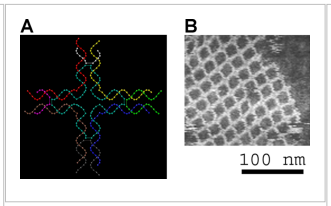
Human Genomics and Biotechnology Applications of DNA Molecular Modeling

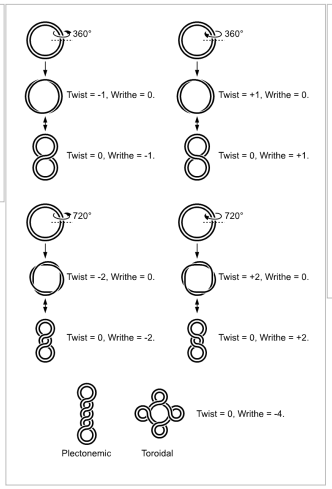
The following two galleries of images illustrate various uses of DNA molecular modeling in Genomics and Biotechnology research applications from DNA repair to PCR and DNA nanostructures; each slide contains its own explanation and/or details. The first slide presents an overview of DNA applications, including DNA molecular models, with emphasis on Genomics and Biotechnology.

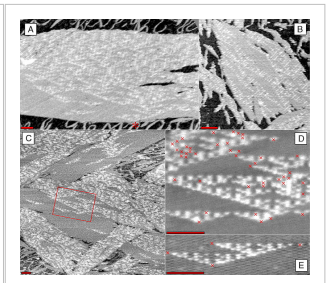
Applications of DNA molecular dynamics computations

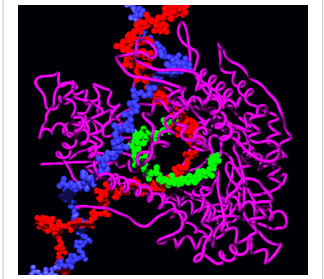
- *First row* images present a DNA biochip and DNA nanostructures designed for DNA computing and other dynamic applications of DNA nanotechnology; last image in this row is of DNA arrays that display a representation of the Sierpinski gasket on their surfaces.
- *Second row*: the first two images show computer molecular models of RNA polymerase, followed by that of an E. coli, bacterial DNA primase template suggesting very complex dynamics at the interfaces between the enzymes and the DNA template; the fourth image illustrates in a computed molecular model the mutagenic, chemical interaction of a potent carcinogen molecule with DNA, and the last image shows the different interactions of specific fluorescence labels with DNA in human and orangoutan chromosomes.

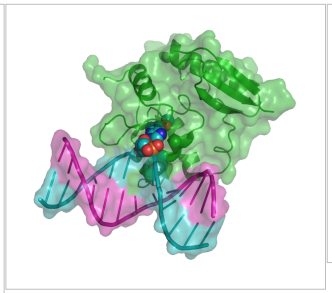


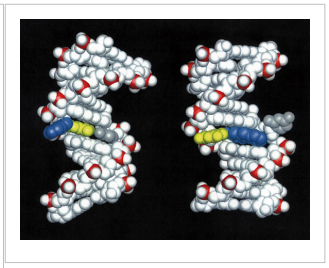












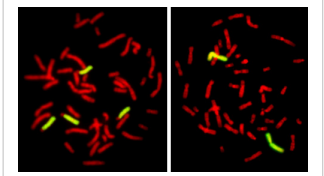
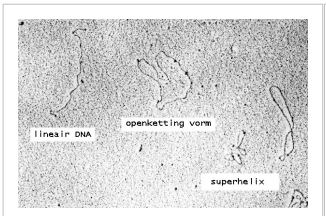
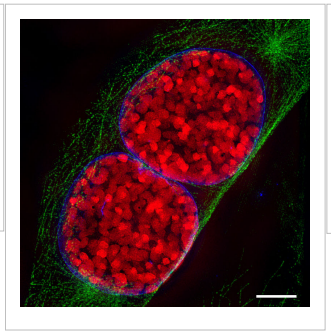
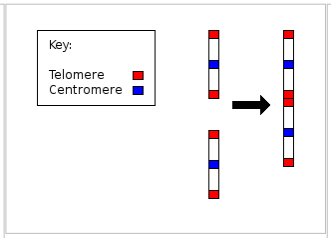


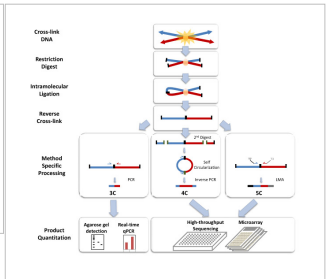
Image Gallery: *DNA Applications and Technologies at various scales in Biotechnology and Genomics research*

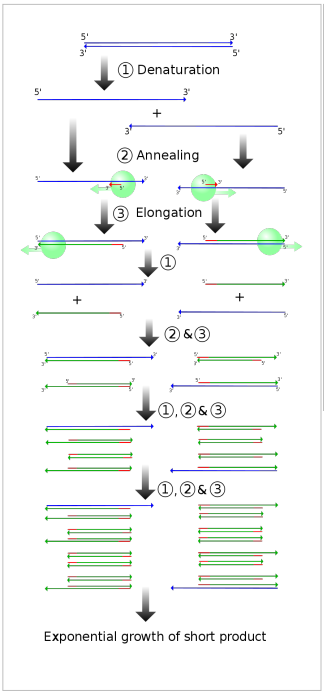
The first figure is an actual electron micrograph of a DNA fiber bundle, presumably of a single plasmid, bacterial DNA loop.

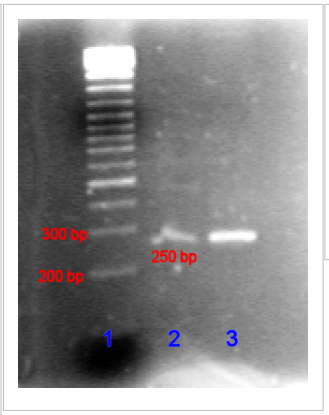


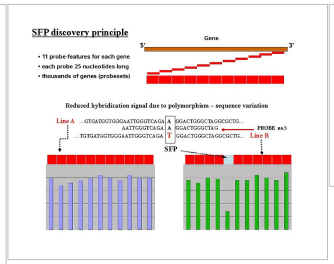


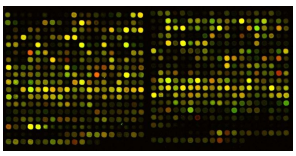


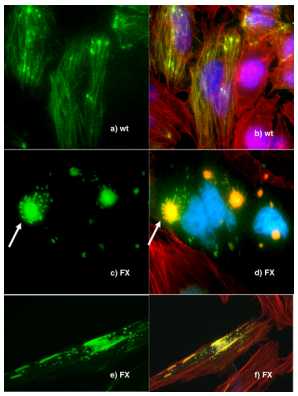


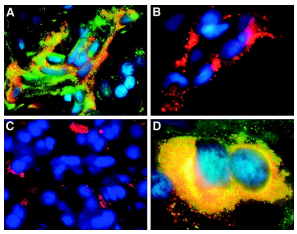

① Denaturation
② Annealing
③ Elongation
①
②&③
①,②&③
①,②&③
Exponential growth of short product

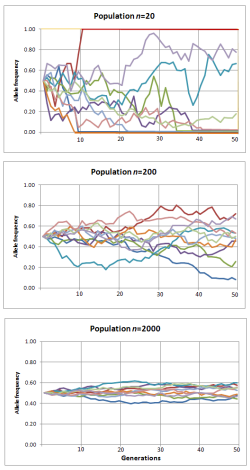

300 bp
250 bp
200 bp
1
2
3

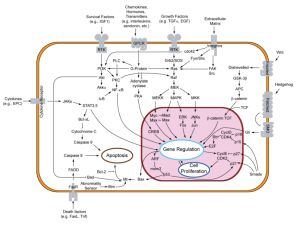

SFP discovery principle
Gene
• 11 probe-features for each gene
• each probe 25 nucleotides long
• thousands of genes (probesets)
Reduced hybridization signal due to polymorphism – sequence variation
Line A
Line B
PROBE no.5
SFP

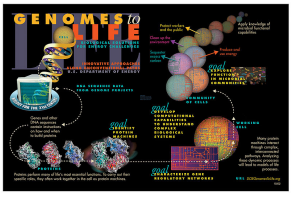



a) wt
b) wt
c) FX
d) FX
e) FX
f) FX


A
B
C
D


Population n=20
Population n=200
Population n=2000
Allele frequency
Generations


Gene Regulation
Apoptosis
Cell Proliferation

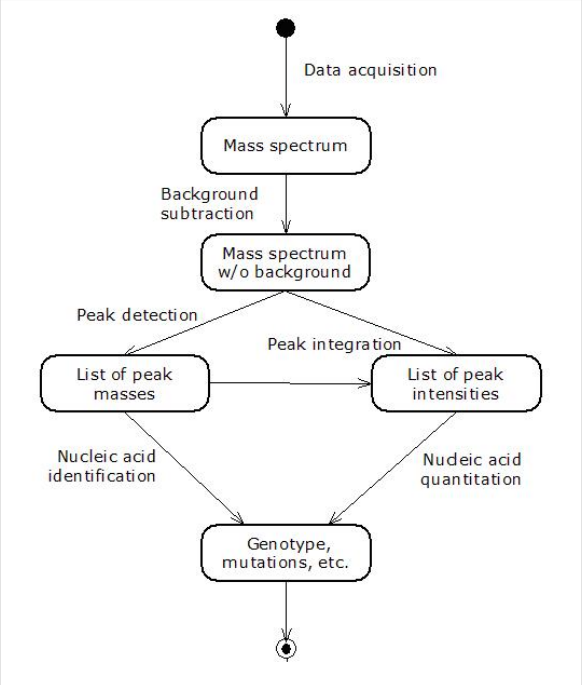

GENOMES to LIFE

Databases for Genomics, DNA Dynamics and Sequencing

Genomic and structural databases

- CBS Genome Atlas Database [14] — contains examples of base skews.[15]
- The Z curve database of genomes — a 3-dimensional visualization and analysis tool of genomes [16][17] .
- DNA and other nucleic acids' molecular models: Coordinate files of nucleic acids molecular structure models in PDB and CIF formats [18]

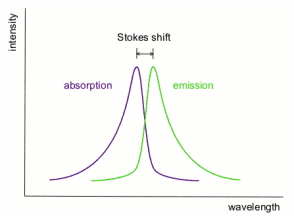
Mass spectrometry--Maldi informatics

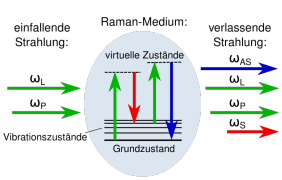


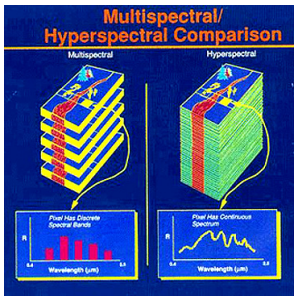
DNA Dynamics Data from Spectroscopy

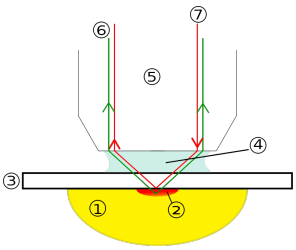
- FT-NMR[19] [20]
  - NMR Atlas--database [21]
  - mmcif downloadable coordinate files of nucleic acids in solution from 2D-FT NMR data [22]
  - NMR constraints files for NAs in PDB format [23]
- NMR microscopy[24]
- Vibrational circular dichroism (VCD)
- Microwave spectroscopy
- FT-IR
- FT-NIR[25] [26] [27]
- Spectral, Hyperspectral, and Chemical imaging)[28] [29] [30] [31] [32] [33] [34] .
- Raman spectroscopy/microscopy[35] and CARS[36] .
- Fluorescence correlation spectroscopy[37] [38] [39] [40] [41] [42] [43] [44] , Fluorescence cross-correlation spectroscopy and FRET[45] [46] [47] .
- Confocal microscopy[48]

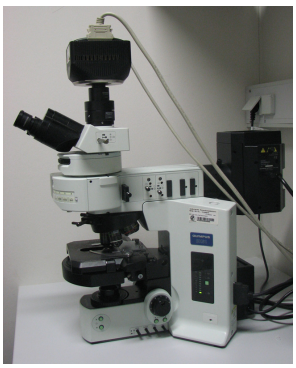
Gallery: CARS (Raman spectroscopy), Fluorescence confocal microscopy, and Hyperspectral imaging

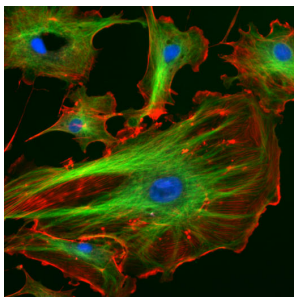


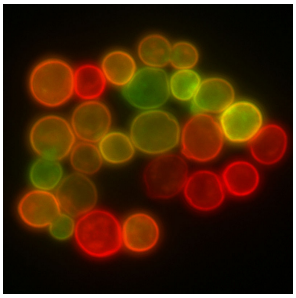


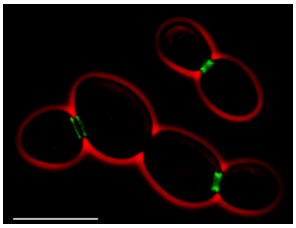


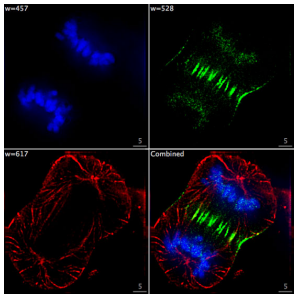


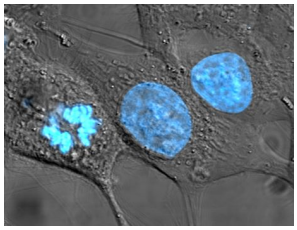


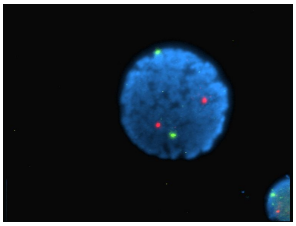


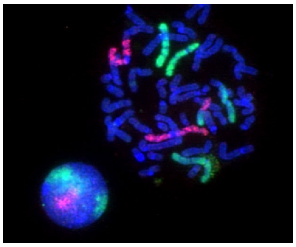


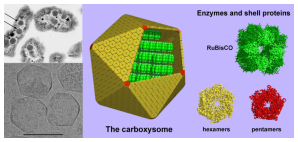












X-ray microscopy

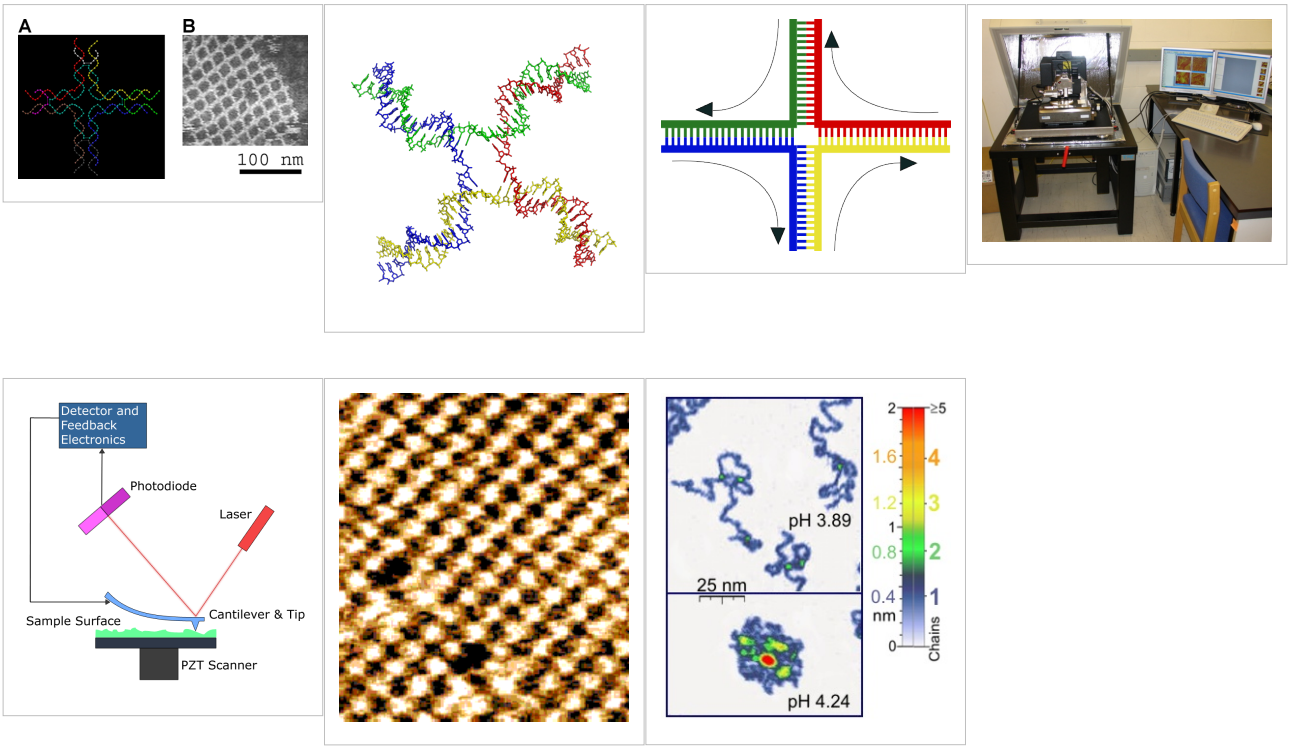
- Application of X-ray microscopy in the analysis of living hydrated cells [49]

Atomic Force Microscopy (AFM)

Two-dimensional DNA junction arrays have been visualized by Atomic Force Microscopy (AFM)[50] . Other imaging resources for AFM/Scanning probe microscopy(SPM) can be freely accessed at:

- How SPM Works [51]
- SPM Image Gallery - AFM STM SEM MFM NSOM and more. [52]

Gallery of AFM Images of DNA Nanostructures



Notes

[1] Franklin, R.E. and Gosling, R.G. recd.6 March 1953. Acta Cryst. (1953). 6, 673 The Structure of Sodium Thymonucleate Fibres I. The Influence of Water Content Acta Cryst. (1953). and 6, 678 The Structure of Sodium Thymonucleate Fibres II. The Cylindrically Symmetrical Patterson Function.

[2] Watson, J.D; Crick F.H.C. 1953a. Molecular Structure of Nucleic Acids- A Structure for Deoxyribose Nucleic Acid., Nature 171(4356):737-738.

[3] Watson, J.D; Crick F.H.C. 1953b. The Structure of DNA., Cold Spring Harbor Symposia on Quantitative Biology 18:123-131.

[4] Wilkins M.H.F., A.R. Stokes A.R. & Wilson, H.R. (1953). " Molecular Structure of Deoxypentose Nucleic Acids (http://www.nature.com/nature/dna50/wilkins.pdf)" (PDF). *Nature* **171**: 738–740. doi: 10.1038/171738a0 (http://dx.doi.org/10.1038/171738a0). PMID 13054693. .

[5] Elson D, Chargaff E (1952). "On the deoxyribonucleic acid content of sea urchin gametes". *Experientia* **8** (4): 143-145.

[6] Chargaff E, Lipshitz R, Green C (1952). "Composition of the deoxypentose nucleic acids of four genera of sea-urchin". *J Biol Chem* **195** (1): 155-160. PMID 14938364.

[7] Chargaff E, Lipshitz R, Green C, Hodes ME (1951). "The composition of the deoxyribonucleic acid of salmon sperm". *J Biol Chem* **192** (1): 223-230. PMID 14917668.

[8] Chargaff E (1951). "Some recent studies on the composition and structure of nucleic acids". *J Cell Physiol Suppl* **38** (Suppl).
[9] Magasanik B, Vischer E, Doniger R, Elson D, Chargaff E (1950). "The separation and estimation of ribonucleotides in minute quantities". *J Biol Chem* **186** (1): 37-50. PMID 14778802.
[10] Chargaff E (1950). "Chemical specificity of nucleic acids and mechanism of their enzymatic degradation". *Experientia* **6** (6): 201-209.
[11] http://ndbserver.rutgers.edu/atlas/xray/structures/U/ud0017/ud0017.html
[12] http://www.phy.cam.ac.uk/research/bss/molbiophysics.php
[13] http://planetphysics.org/encyclopedia/TheoreticalBiophysics.html
[14] http://www.cbs.dtu.dk/services/GenomeAtlas/
[15] Hallin PF, David Ussery D (2004). "CBS Genome Atlas Database: A dynamic storage for bioinformatic results and DNA sequence data". *Bioinformatics* **20**: 3682-3686.
[16] http://tubic.tju.edu.cn/zcurve/
[17] Zhang CT, Zhang R, Ou HY (2003). "The Z curve database: a graphic representation of genome sequences". Bioinformatics 19 (5): 593-599. doi:10.1093/bioinformatics/btg041
[18] http://ndbserver.rutgers.edu/ftp/NDB/models/
[19] (http://www.jonathanpmiller.com/Karplus.html)- obtaining dihedral angles from ^{3}J coupling constants
[20] (http://www.spectroscopynow.com/FCKeditor/UserFiles/File/specNOW/HTML files/General_Karplus_Calculator.htm) Another Javascript-like NMR coupling constant to dihedral
[21] http://ndbserver.rutgers.edu/atlas/nmr/index.html
[22] http://ndbserver.rutgers.edu/ftp/NDB/coordinates/na-nmr-mmcif/
[23] http://ndbserver.rutgers.edu/ftp/NDB/nmr-restraints/
[24] Lee, S. C. et al., (2001). One Micrometer Resolution NMR Microscopy. *J. Magn. Res.*, **150**: 207-213.
[25] Near Infrared Microspectroscopy, Fluorescence Microspectroscopy,Infrared Chemical Imaging and High Resolution Nuclear Magnetic Resonance Analysis of Soybean Seeds, Somatic Embryos and Single Cells., Baianu, I.C. et al. 2004., In *Oil Extraction and Analysis.*, D. Luthria, Editor pp.241-273, AOCS Press., Champaign, IL.
[26] Single Cancer Cell Detection by Near Infrared Microspectroscopy, Infrared Chemical Imaging and Fluorescence Microspectroscopy.2004.I. C. Baianu, D. Costescu, N. E. Hofmann and S. S. Korban, q-bio/0407006 (July 2004) (http://arxiv.org/abs/q-bio/0407006)
[27] Raghavachari, R., Editor. 2001. *Near-Infrared Applications in Biotechnology*, Marcel-Dekker, New York, NY.
[28] http://www.imaging.net/chemical-imaging/ Chemical imaging
[29] http://www.malvern.com/LabEng/products/sdi/bibliography/sdi_bibliography.htm E. N. Lewis, E. Lee and L. H. Kidder, Combining Imaging and Spectroscopy: Solving Problems with Near-Infrared Chemical Imaging. Microscopy Today, Volume 12, No. 6, 11/2004.
[30] D.S. Mantus and G. H. Morrison. 1991. Chemical imaging in biology and medicine using ion microscopy., *Microchimica Acta*, **104**, (1-6) January 1991, doi: 10.1007/BF01245536
[31] Near Infrared Microspectroscopy, Fluorescence Microspectroscopy,Infrared Chemical Imaging and High Resolution Nuclear Magnetic Resonance Analysis of Soybean Seeds, Somatic Embryos and Single Cells., Baianu, I.C. et al. 2004., In *Oil Extraction and Analysis.*, D. Luthria, Editor pp.241-273, AOCS Press., Champaign, IL.
[32] Single Cancer Cell Detection by Near Infrared Microspectroscopy, Infrared Chemical Imaging and Fluorescence Microspectroscopy.2004.I. C. Baianu, D. Costescu, N. E. Hofmann and S. S. Korban, q-bio/0407006 (July 2004) (http://arxiv.org/abs/q-bio/0407006)
[33] J. Dubois, G. Sando, E. N. Lewis, Near-Infrared Chemical Imaging, A Valuable Tool for the Pharmaceutical Industry, G.I.T. Laboratory Journal Europe, No.1-2, 2007.
[34] Applications of Novel Techniques to Health Foods, Medical and Agricultural Biotechnology.(June 2004).,I. C. Baianu, P. R. Lozano, V. I. Prisecaru and H. C. Lin q-bio/0406047 (http://arxiv.org/abs/q-bio/0406047)
[35] Chemical Imaging Without Dyeing (http://witec.de/en/download/Raman/ImagingMicroscopy04.pdf)
[36] C.L. Evans and X.S. Xie.2008. Coherent Anti-Stokes Raman Scattering Microscopy: Chemical Imaging for Biology and Medicine., doi:10.1146/annurev.anchem.1.031207.112754 *Annual Review of Analytical Chemistry*, **1**: 883-909.
[37] Eigen, M., Rigler, M. Sorting single molecules: application to diagnostics and evolutionary biotechnology,(1994) *Proc. Natl. Acad. Sci. USA*, 91,5740-5747.
[38] Rigler, M. Fluorescence correlations, single molecule detection and large number screening. Applications in biotechnology,(1995) J. Biotechnol., 41,177-186.
[39] Rigler R. and Widengren J. (1990). Ultrasensitive detection of single molecules by fluorescence correlation spectroscopy, *BioScience* (Ed. Klinge & Owman) p.180.

[40] Single Cancer Cell Detection by Near Infrared Microspectroscopy, Infrared Chemical Imaging and Fluorescence Microspectroscopy.2004.I. C. Baianu, D. Costescu, N. E. Hofmann, S. S. Korban and et al., q-bio/0407006 (July 2004) (http://arxiv.org/abs/q-bio/0407006)
[41] Oehlenschläger F., Schwille P. and Eigen M. (1996). Detection of HIV-1 RNA by nucleic acid sequence-based amplification combined with fluorescence correlation spectroscopy, *Proc. Natl. Acad. Sci. USA* **93**:1281.
[42] Bagatolli, L.A., and Gratton, E. (2000). Two-photon fluorescence microscopy of coexisting lipid domains in giant unilamellar vesicles of binary phospholipid mixtures. Biophys J., 78:290-305.
[43] Schwille, P., Haupts, U., Maiti, S., and Webb. W.(1999). Molecular dynamics in living cells observed by fluorescence correlation spectroscopy with one- and two-photon excitation. Biophysical Journal, 77(10):2251-2265.
[44] Near Infrared Microspectroscopy, Fluorescence Microspectroscopy,Infrared Chemical Imaging and High Resolution Nuclear Magnetic Resonance Analysis of Soybean Seeds, Somatic Embryos and Single Cells., Baianu, I.C. et al. 2004., In *Oil Extraction and Analysis.*, D. Luthria, Editor pp.241-273, AOCS Press., Champaign, IL.
[45] FRET description (http://dwb.unl.edu/Teacher/NSF/C08/C08Links/pps99.cryst.bbk.ac.uk/projects/gmocz/fret.htm)
[46] doi:10.1016/S0959-440X(00)00190-1 (http://dx.doi.org/10.1016/S0959-440X(00)00190-1)Recent advances in FRET: distance determination in protein–DNA complexes. *Current Opinion in Structural Biology* **2001**, *11(2)*, 201-207
[47] http://www.fretimaging.org/mcnamaraintro.html FRET imaging introduction
[48] Eigen, M., and Rigler, R. (1994). Sorting single molecules: Applications to diagnostics and evolutionary biotechnology, Proc. Natl. Acad. Sci. USA 91:5740.
[49] http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12379938
[50] Mao, Chengde; Sun, Weiqiong & Seeman, Nadrian C. (16 June 1999). "Designed Two-Dimensional DNA Holliday Junction Arrays Visualized by Atomic Force Microscopy". *Journal of the American Chemical Society* **121** (23): 5437–5443. doi: 10.1021/ja9900398 (http://dx.doi.org/10.1021/ja9900398). ISSN 0002-7863 (http://worldcat.org/issn/0002-7863).
[51] http://www.parkafm.com/New_html/resources/01general.php
[52] http://www.rhk-tech.com/results/showcase.php

References

- Sir Lawrence Bragg, FRS. *The Crystalline State, A General survey.* London: G. Bells and Sons, Ltd., vols. 1 and 2., 1966., 2024 pages.
- F. Bessel, *Untersuchung des Theils der planetarischen Störungen*, Berlin Abhandlungen (1824), article 14.
- Cantor, C. R. and Schimmel, P.R. *Biophysical Chemistry, Parts I and II.*, San Franscisco: W.H. Freeman and Co. 1980. 1,800 pages.
- Eigen, M., and Rigler, R. (1994). Sorting single molecules: Applications to diagnostics and evolutionary biotechnology, *Proc. Natl. Acad. Sci. USA* **91**:5740.
- Raghavachari, R., Editor. 2001. *Near-Infrared Applications in Biotechnology*, Marcel-Dekker, New York, NY.
- Rigler R. and Widengren J. (1990). Ultrasensitive detection of single molecules by fluorescence correlation spectroscopy, *BioScience* (Ed. Klinge & Owman) p.180.
- *Applications of Novel Techniques to Health Foods, Medical and Agricultural Biotechnology.*(June 2004) I. C. Baianu, P. R. Lozano, V. I. Prisecaru and H. C. Lin., q-bio/0406047.
- Single Cancer Cell Detection by Near Infrared Microspectroscopy, Infrared Chemical Imaging and Fluorescence Microspectroscopy.2004. I. C. Baianu, D. Costescu, N. E. Hofmann, S. S. Korban and et al., q-bio/0407006 (July 2004).
- Voet, D. and J.G. Voet. *Biochemistry*, 2nd Edn., New York, Toronto, Singapore: John Wiley & Sons, Inc., 1995, ISBN: 0-471-58651-X., 1361 pages.

- Watson, G. N. *A Treatise on the Theory of Bessel Functions.*, (1995) Cambridge University Press. ISBN 0-521-48391-3.
- Watson, James D. and Francis H.C. Crick. A structure for Deoxyribose Nucleic Acid (http://www.nature.com/nature/dna50/watsoncrick.pdf) (PDF). *Nature* 171, 737–738, 25 April 1953.
- Watson, James D. *Molecular Biology of the Gene.* New York and Amsterdam: W.A. Benjamin, Inc. 1965., 494 pages.
- Wentworth, W.E. *Physical Chemistry. A short course.*, Malden (Mass.): Blackwell Science, Inc. 2000.
- Herbert R. Wilson, FRS. *Diffraction of X-rays by proteins, Nucleic Acids and Viruses.*, London: Edward Arnold (Publishers) Ltd. 1966.
- Kurt Wuthrich. *NMR of Proteins and Nucleic Acids.*, New York, Brisbane,Chicester, Toronto, Singapore: J. Wiley & Sons. 1986., 292 pages.
- Robinson, Bruche H.; Seeman, Nadrian C. (August 1987). "The Design of a Biochip: A Self-Assembling Molecular-Scale Memory Device". *Protein Engineering* **1** (4): 295–300. ISSN 0269-2139 (http://worldcat.org/issn/0269-2139). Link (http://peds.oxfordjournals.org/cgi/content/abstract/1/4/295)
- Rothemund, Paul W. K.; Ekani-Nkodo, Axel; Papadakis, Nick; Kumar, Ashish; Fygenson, Deborah Kuchnir & Winfree, Erik (22 December 2004). "Design and Characterization of Programmable DNA Nanotubes". *Journal of the American Chemical Society* **126** (50): 16344–16352. doi: 10.1021/ja044319l (http://dx.doi.org/10.1021/ja044319l). ISSN 0002-7863 (http://worldcat.org/issn/0002-7863).
- Keren, K.; Kinneret Keren, Rotem S. Berman, Evgeny Buchstab, Uri Sivan, Erez Braun (November 2003). " DNA-Templated Carbon Nanotube Field-Effect Transistor (http://www.sciencemag.org/cgi/content/abstract/sci;302/5649/1380)". *Science* **302** (6549): 1380–1382. doi: 10.1126/science.1091022 (http://dx.doi.org/10.1126/science.1091022). ISSN 1095-9203 (http://worldcat.org/issn/1095-9203). http://www.sciencemag.org/cgi/content/abstract/sci;302/5649/1380.
- Zheng, Jiwen; Constantinou, Pamela E.; Micheel, Christine; Alivisatos, A. Paul; Kiehl, Richard A. & Seeman Nadrian C. (2006). "2D Nanoparticle Arrays Show the Organizational Power of Robust DNA Motifs". *Nano Letters* **6**: 1502–1504. doi: 10.1021/nl060994c (http://dx.doi.org/10.1021/nl060994c). ISSN 1530-6984 (http://worldcat.org/issn/1530-6984).
- Cohen, Justin D.; Sadowski, John P.; Dervan, Peter B. (2007). "Addressing Single Molecules on DNA Nanostructures". *Angewandte Chemie* **46** (42): 7956–7959. doi: 10.1002/anie.200702767 (http://dx.doi.org/10.1002/anie.200702767). ISSN 0570-0833 (http://worldcat.org/issn/0570-0833).
- Mao, Chengde; Sun, Weiqiong & Seeman, Nadrian C. (16 June 1999). "Designed Two-Dimensional DNA Holliday Junction Arrays Visualized by Atomic Force Microscopy". *Journal of the American Chemical Society* **121** (23): 5437–5443. doi: 10.1021/ja9900398 (http://dx.doi.org/10.1021/ja9900398). ISSN 0002-7863 (http://worldcat.org/issn/0002-7863).
- Constantinou, Pamela E.; Wang, Tong; Kopatsch, Jens; Israel, Lisa B.; Zhang, Xiaoping; Ding, Baoquan; Sherman, William B.; Wang, Xing; Zheng, Jianping; Sha, Ruojie & Seeman, Nadrian C. (2006). "Double cohesion in structural DNA nanotechnology". *Organic and Biomolecular Chemistry* **4**: 3414–3419. doi: 10.1039/b605212f (http://dx.doi.org/10.1039/b605212f).

See also

- DNA
- Molecular modeling of DNA
- Genomics
- Signal transduction
- Transcriptomics
- → Interactomics
- Biotechnology
- → Molecular graphics
- Quantum computing
- MAYA-II
- DNA computing
- DNA structure
- Molecular structure
- → Molecular dynamics
- → Molecular topology
- DNA topology
- DNA, the Genome and Interactome
- Molecular structure
- Molecular geometry fluctuations
- Molecular interactions
- → Molecular topology
- Hydrogen bonding
- Hydrophobic interactions
- DNA dynamics and conformations
- DNA Conformational isomerism
- 2D-FT NMRI and Spectroscopy
- Paracrystalline lattices/Paracrystals
- NMR Spectroscopy
- VCD or Vibrational circular dichroism
- Microwave spectroscopy
- Two-dimensional IR spectroscopy
- FRET and FCS- Fluorescence correlation spectroscopy
- Fluorescence cross-correlation spectroscopy (FCCS)
- Spectral imaging
- Hyperspectral imaging
- Chemical imaging
- NMR microscopy
- X-ray scattering
- Neutron scattering
- Crystallography
- Crystal lattices
- Molecular geometry
- Nanostructure
- DNA nanotechnology
- Imaging
- Sirius visualization software

- Atomic force microscopy
- X-ray microscopy
- Liquid crystals
- Glasses
- QMC@Home
- Sir Lawrence Bragg, FRS
- Sir John Randall
- Francis Crick
- Manfred Eigen
- Felix Bloch
- Paul Lauterbur
- Maurice Wilkins
- Herbert Wilson, FRS
- Alex Stokes

External links

- DNAlive: a web interface to compute DNA physical properties (http://mmb.pcb.ub.es/DNAlive). Also allows cross-linking of the results with the UCSC Genome browser and DNA dynamics.
- Application of X-ray microscopy in analysis of living hydrated cells (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12379938)
- DiProDB: Dinucleotide Property Database (http://diprodb.fli-leibniz.de). The database is designed to collect and analyse thermodynamic, structural and other dinucleotide properties.
- DNA the Double Helix Game (http://nobelprize.org/educational_games/medicine/dna_double_helix/) From the official Nobel Prize web site
- MDDNA: Structural Bioinformatics of DNA (http://humphry.chem.wesleyan.edu:8080/MDDNA/)
- Double Helix 1953–2003 (http://www.ncbe.reading.ac.uk/DNA50/) National Centre for Biotechnology Education
- DNA under electron microscope (http://www.fidelitysystems.com/Unlinked_DNA.html)
- Further details of mathematical and molecular analysis of DNA structure based on X-ray data (http://planetphysics.org/encyclopedia/BesselFunctionsApplicationsToDiffractionByHelicalStructures.html)
- Bessel functions corresponding to Fourier transforms of atomic or molecular helices. (http://planetphysics.org/?op=getobj&from=objects&name=BesselFunctionsAndTheirApplicationsToDiffractionByHelicalStructures)
- Characterization in nanotechnology some pdfs (http://nanocharacterization.sitesled.com/)
- An overview of STM/AFM/SNOM principles with educative videos (http://www.ntmdt.ru/SPM-Techniques/Principles/)
- SPM Image Gallery - AFM STM SEM MFM NSOM and More (http://www.rhk-tech.com/results/showcase.php)
- How SPM Works (http://www.parkafm.com/New_html/resources/01general.php)
- U.S. National DNA Day (http://www.genome.gov/10506367) — watch videos and participate in real-time discusssions with scientists.

- The Secret Life of DNA - DNA Music compositions (http://www.tjmitchell.com/stuart/dna.html)
- Ascalaph DNA (http://www.agilemolecule.com/Ascalaph/Ascalaph_DNA.html) — Commercial software for DNA modeling

Metastability in the brain

In the field of computational neuroscience, the theory of **metastability** refers to the human brain's ability to integrate several functional parts and to produce neural oscillations in a cooperative and coordinated manner, providing the basis for conscious activity.

Metastability, a state in which signals (such as oscillatory waves), fall outside their natural equilibrium state but persist for an extended period of time, is a principle that describes the brain's ability to make sense out of seemingly random environmental cues. In the past 25 years, interest in metastability and the underlying framework of nonlinear dynamics has been fueled by advancements in the methods by which computers model brain activity.

Overview

EEG and EMG are used to model brain output as waveforms. In the metastability theory, EEG outputs produce oscillations that can be described as having identifiable patterns that correlate with each other at certain frequencies. Each neuron in a neuronal network normally outputs a dynamical oscillatory waveform, but also has the ability to output a chaotic waveform [1] . When neurons are integrated into the neural network by interfacing neurons with each other, the dynamical oscillations created by each neuron can be combined to form highly predictable EEG oscillations.

By identifying these correlations and the individual neurons that contribute to predictable EEG oscillations, scientists can determine which cortical domains are processing in parallel and which neuronal networks are intertwined. In many cases, metastability describes instances in which distal parts of the brain interact with each other to respond to environmental stimuli.

Frequency Domains of Metastability

It has been suggested that one integral facet of brain dynamics underlying conscious thought is the brain's ability to convert seemingly noisy or chaotic signals into predictable oscillatory patterns[2] .

In EEG oscillations of neural networks, neighboring waveform frequencies are correlated on a logarithmic scale rather than a linear scale. As a result, mean frequencies in oscillatory bands cannot link together according to linearity of their mean frequencies. Instead, phase transitions are linked according to their ability to couple with adjacent phase shifts in a constant state of transition between unstable and stable phase synchronization[2] . This phase synchronization forms the basis of metastable behavior in neural networks.

Metastable behavior occurs at the high frequency domain known as ***1/f regime***. This regime describes an environment in which a noisy signal (also known as pink noise) has been induced, where the amount of power the signal outputs over a certain bandwidth (its

power spectral density) is inversely proportional to its frequency.

Noise at the *1/f* regime can be found in many biological systems – for instance, in the output of a heartbeat in an ECG waveform -- but serves a unique purpose for phase synchrony in neural networks. At the *1/f* regime, the brain is in the critical state necessary for a conscious response to weak or chaotic environmental signals because it can shift the random signals into identifiable and predictable oscillatory waveforms [2] . While often transient, these waveforms exist in a stable form long enough to contribute to what can be thought of as conscious response to environmental stimuli.

Theories of Metastability

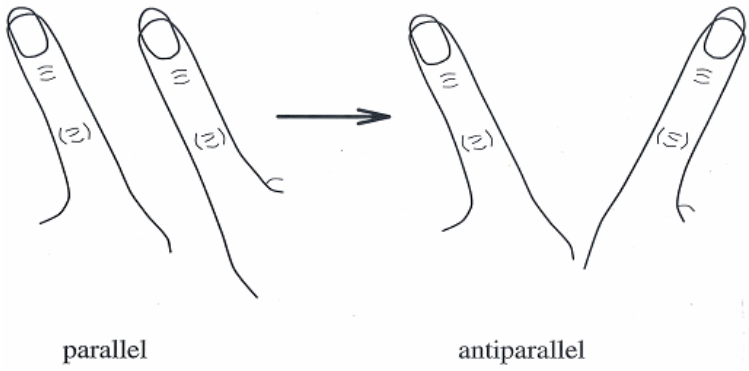
Oscillatory Activity and Coordination Dynamics

The dynamical system model, which represents networks composed of integrated neural systems communicating with one another between unstable and stable phases, has become an increasingly popular theory underpinning the understanding of metastability [3] . Coordination dynamics forms the basis for this dynamical system model by describing mathematical formulae and paradigms governing the coupling of environmental stimuli to their effectors[4] .

History of Coordination Dynamics and the Haken-Kelso-Bunz (HKB) Model

The so-named HKB model is one of the earliest and well-respected theories to describe coordination dynamics in the brain. In this model, the formation of neural networks can be partly described as self-organization, where individual neurons and small neuronal systems aggregate and coordinate to either adapt or respond to local stimuli or to divide labor and specialize in function[5] .

In the last 20 years, the HKB model has become a widely-accepted theory to explain the coordinated movements and behaviors of individual neurons into large, end-to-end neural networks. Originally the model described a system in which spontaneous transitions observed in finger movements could be described as a series of in-phase and out-of-phase movements[6] .



Transition of parallel movement of index fingers to antiparallel, symmetric movement.

In the mid-1980s HKB model experiments, subjects were asked to wave one finger on each hand in two modes of direction: first, known as out of phase, both fingers moving in the same direction back and forth (as windshield wipers might move); and second, known as in-phase, where both fingers come together and move away to and from the midline of the body. To illustrate coordination dynamics, the subjects were asked to move their fingers out of phase with increasing speed until their fingers were moving as fast as possible. As movement approached its critical speed, the subjects' fingers were found to move from out-of-phase (windshield-wiper-like) movement to in-phase (toward midline movement).

The HKB model, which has also been elucidated by several complex mathematical descriptors, is still a relatively simple but powerful way to describe seemingly-independent systems that come to reach synchrony just before a state of self-organized criticality[6] [7] .

Evolution of Cognitive Coordination Dynamics

In the last 10 years, the HKB model has been reconciled with advanced mathematical models and supercomputer-based computation to link rudimentary coordination dynamics to higher-order processes such as learning and memory.

The traditional EEG is still useful to investigate coordination between different parts of the brain. 40 Hz gamma wave activity is a prominent example of the brain's ability to be modeled dynamically and is a common example of coordination dynamics. Continuous study of these and other oscillations has led to an important conclusion: analyzing waves as having a common signal phase but a different amplitude leads to the possibility that these different signals serve a synergistic function [8] .

It is interesting to note some unusual characteristics of these waves: they are virtually simultaneous and have a very short onset latency, which implies that they operate faster than synaptic conduction would allow; and that their recognizable patterns are sometimes interrupted by periods of randomness. The latter idiosyncrasy has served as the basis for assuming an interaction and transition between neural subsystems. Analysis of activation and deactivation of regions of the cortex has shown a dynamic shift between dependence and interdependence, reflecting the brain's *metastable* nature as a function of a coordinated dynamical system.

fMRI, large-scale electrode arrays, and MEG expand upon the patterns seen in EEG by providing visual confirmation of coordinated dynamics. The fMRI, which provides an improvement over EEG in spatiotemporal characterization, allows researchers to stimulate certain parts of the brain with environmental cues and observe the response in a holistic brain model. Additionally, the fMRI has a response time of about one millisecond, allowing for a virtually real-time investigation of the active turning –on and –off of selected parts of the brain in response to environmental cues and conscious tasks[9] .

Social Coordination Dynamics and the Phi Complex

A developing field in coordination dynamics involves the theory of social coordination, which attempts to relate the DC to normal human development of complex social cues following certain patterns of interaction. This work is aimed at understanding how human social interaction is mediated by metastability of neural networks. fMRI and EEG are particularly useful in mapping thalamocortical response to social cues in experimental studies.

A new theory called the Phi complex has been developed by J. A. Scott Kelso and fellow researchers at Florida Atlantic University to provide experimental results for the theory of social coordination dynamics[10] . In Kelso's experiments, two subjects were separated by an opaque barrier and asked to wag their fingers; then the barrier was removed and the subjects were instructed to continue to wag their fingers as if no change had occurred. After a short period, the movements of the two subjects sometimes became coordinated and synchronized (but other times continued to be asynchronous). The link between EEG and conscious social interaction is described as Phi, one of several brain rhythms operating in the 10 Hz range. Phi consists of two components: one to favor solitary behavior and another

to favor interactive (interpersonal) behavior. Further analysis of Phi may reveal the social and interpersonal implications of degenerative diseases such as schizophrenia -- or may provide insight into common social relationships such as the dynamics of alpha and omega-males or the popular bystander effect describing how people diffuse personal responsibility in emergency situations depending on the number of other individuals present.

The Dynamic Core

A second theory of metastability involves a so-called **dynamic core**, which is a term to loosely describe the thalamocortical region believed to be the integration center of consciousness. The dynamic core hypothesis (DCH) reflects the use and disuse of interconnected neuronal networks during stimulation of this region. A computer model of 65,000 spiking neurons[8] shows that neuronal groups existing in the cortex and thalamus interact in the form of synchronous oscillation. The interaction between distinct neuronal groups forms the dynamic core and may help explain the nature of conscious experience. A critical feature of the DCH is that instead of thinking binarily about transitions between neural integration and non-integration (i.e., that the two are either one or the other with no in-between), the metastable nature of the dynamic core can allow for a continuum of integration[8] .

Neural Darwinism

One theory used to integrate the dynamic core with conscious thought involves a developing concept known as neural Darwinism[11] . In this model, metastable interactions in the thalamocortical region cause a process of selectionism through re-entry (a phenomenon describing the overall reciprocity and interactivity between signals in distant parts of the brain through coupled signal latency). Neuronal selectivity involves mechanochemical events that take place pre- and post-natally whereby neuronal connections are influenced by environmental experiences[12] . The modification of synaptic signals as it relates to the dynamic core provides further explanation for the DCH.

Despite growing evidence for the DCH, the ability to generate mathematical constructs to model and predict dynamic core behavior has been slow to progress[13] . Continued development of stochastic processes designed to graph neuronal signals as chaotic and non-linear has provided some algorithmic basis for analyzing how chaotic environmental signals are coupled to enhance selectivity of neural outgrowth or coordination in the dynamic core.

The Global Workspace Hypothesis

The global workspace hypothesis is another theory to elucidate metastability, and has existed in some form since 1983[14] . This hypothesis focuses again on re-entry, the ability of a routine or process to be used by multiple parts of the brain simultaneously[8] . Both the DC and global neuronal workspace (GNW) models involve re-entrance, but the GNW model elaborates on re-entrant connectivity between distant parts of the brain and long-range signal flow. Workspace neurons are similar anatomically but separated spatially from each other.

One interesting aspect of the GNW is that with sufficient intensity and length over which a signal travels, a small initiation signal can be compounded to activate an "ignition" of a

critical spike-inducing state. This idea is analogous to a skier on the slope of a mountain, who, by disrupting a few blocks of ice with his skis, initiates a giant avalanche in his wake. To help prove the circuit-like amplification theory, research has shown that inducing lesions in long-distance connections corrupts performance in integrative models[8] .

A popular experiment to demonstrate the global workspace hypothesis involves showing a subject a series of backward-masked visual words (e.g., "*the dog sleeps quietly*" is shown as "*ylteiuq speels god eht*") and then asking the subject to identify the forward "translation" of these words. Not only did fMRI detect activity in the word-recognition portion of the cortex, but additionally, activity is often detected in the parietal and prefrontal cortices[15] . In almost every experiment, conscious input in word and audition tasks shows a much wider use of integrated portions of the brain than in identical unconscious input. The wide distribution and constant signal transfer between different areas of the brain in experimental results is a common method to attempt to prove the neural workspace hypothesis. More studies are being conducted to determine precisely the correlation between conscious and unconscious task deliberation in the realm of the global workspace.

The Operational Architectonics Theory of Brain-Mind

Although the concept of metastability has been around in the Neuroscience for some time [16] , the specific interpretation of metastability in the context of brain operations of different complexity has been developed by Andrew and Alexander Fingelkurts. Metastability is basically a theory of how global integrative and local segregative tendencies coexist in the brain [17] [18] . The Operational Architectonics is centered around the fact that in the metastable regime of brain functioning, the individual parts of the brain exhibit tendencies to function autonomously at the same time as they exhibit tendencies for coordinated activity [19] [20] . In accrodence with Operational Architectonics [21], the synchronized operations produced by distributed neuronal assemblies constitute the metastable spatial-temporal patterns. They are metastable because intrinsic differences in the activity between neuronal assemblies are sufficiently large that they do each their own job (operation), while still retaining a tendency to be coordinated together in order to realize the complex brain operation [22] [23] .

The Future of Metastability

In addition to study investigating the effects of metastable interactions on traditional social function, much research will likely focus on determining the role of the coordinated dynamic system and the global workspace in the progression of debilitating diseases such as Alzheimer’s Disease, Parkinson's Disease, stroke, and schizophrenia[24] . Undoubtedly, spatiotemporal imaging techniques such as MEG and fMRI will elaborate on results already gleaned from analysis of EEG output.

An interest in the effect of a traumatic or semi-traumatic brain injury (TBI) on the coordinated dynamical system has developed in the last five years as the number of TBI cases has risen from war-related injuries.

See also

- Consciousness
- Cognitive Psychology
- Computational Neuroscience
- Electroencephalogram
- Functional MRI
- Magnetoencephalography
- Neural Darwinism
- Self-organization

References

[1] Thiran, P; M Hasler (1994-12-18). "Information processing using stable and unstable oscillations: a tutorial". *Cellular Neural Networks and their Applications*: 127–136.

[2] Buzsáki, György (2006). *Rhythms of the Brain*. U.S.: Oxford University Press. pp. 128–31. ISBN 0195301064.

[3] Fingelkurts, A.; A. Fingelkurts (2004). "Making complexity simpler: Multivariability and metastability in the brain.". *Intern. J. Neuroscience* **114** (114): 843–862. doi: 10.1080/00207450490450046 (http://dx.doi.org/10.1080/00207450490450046).|url=|format=PDF|accessdate=2007-11-25

[4] "Laboratory for Coordination Dynamics - Center for Complex Systems and Brain Sciences" (http://www.ccs.fau.edu/html_old/coordlab.htm). *Florida Atlantic University*. . Retrieved on 2007-11-27.

[5] Collier, T.; Charles Taylor (2004-07). "Self-organization in sensor networks.". *J. Parallel and Distributed Computing* **64** (7): 866–873. doi: 10.1016/j.jpdc.2003.12.004 (http://dx.doi.org/10.1016/j.jpdc.2003.12.004).|url=http://www.isrl.uiuc.edu/~amag/langev/paper/collier04sensorNetworks.html|format=PDF|accessdate=2007-11-26

[6] Fuchs, A.; V.K. Jirsa (2000). "The HKB model revisited: How varying the degree of symmetry controls dynamics". *Human Movement Science* **19** (4): 425–449. doi: 10.1016/S0167-9457(00)00025-7 (http://dx.doi.org/10.1016/S0167-9457(00)00025-7).

[7] Kelso, J.A. Scott; et al. (1988). "Dynamic pattern generation in behavioral and neural systems". *Science* **239** (4847): 1513–1520. doi: 10.1126/science.3281253 (http://dx.doi.org/10.1126/science.3281253). PMID 3281253.|url=|format=PDF|accessdate=2007-11-26

[8] Werner, A. G.; V.K. Jirsa (2007-09). "Metastability, criticality and phase transitions in brain and its models". *Biosystems* **90** (2): 496–508. doi: 10.1016/j.biosystems.2006.12.001 (http://dx.doi.org/10.1016/j.biosystems.2006.12.001).|url=|format=PDF|accessdate=2007-11-26

[9] Jirsa, V.K.; A. Fuchs, J.A.S. Kelso, (1998-11). "Connecting Cortical and behavioral dynamics: bimanual coordination". *Neural Computation* **10** (8): 2019–2045. doi: 10.1162/089976698300016954 (http://dx.doi.org/10.1162/089976698300016954).|url=|format=PDF|accessdate=2007-11-26

[10] Tognoli, E; et al. (2007-03). "The phi complex as a neuromarker of human social coordination". *PNAS* **104** (19): 8190–8195. doi: 10.1073/pnas.0611453104 (http://dx.doi.org/10.1073/pnas.0611453104). PMID 17470821.

[11] Seth, A.; B. Baars (2005). "Neural Darwinism and consciousness". *Consciousness and Cognition* (14): 140–168.

[12] Edelman, Gerald (1987). *Neural Darwinism: The Theory of Neuronal Group Selection*. New York, New York: Basic Books. ISBN 0-19-286089-5.

[13] Le Van Quyen, M. (2003). "Disentangling the dynamic core: a research program for a neurodynamics at the large-scale". *Biol. Res.* **36** (1): 67–88.

[14] Baars, Bernard (2003-10). "An update on global workspace theory" (http://cogweb.ucla.edu/CogSci/Baars-update_03.html). *Science and Consciousness Review*. . Retrieved on 2007-11-26.

[15] DeHaene, S.; L. Naccache (2001). "Toward a cognitive neuroscience of consciousness: basic evidence and a workspace framework". *Cognition* **39** (1): 1–37. doi: 10.1016/S0010-0277(00)00123-2 (http://dx.doi.org/10.1016/S0010-0277(00)00123-2).|url=http://www.ingentaconnect.com/els/00100277/2001/00000079/00000001/art00123|format=|accessdate=2007-11-26

[21] http://www.bm-science.com/team/chapt3.pdf

[24] "The Human Brain and Behavior Laboratory" (http://www.ccs.fau.edu/section_links/HBBLv2/). *Center for Complex Systems and Brain Sciences - Florida Atlantic University*. . Retrieved on 2007-11-26.

External links

- The Human Brain and Behavior Laboratory (http://www.ccs.fau.edu/section_links/HBBLv2/) - Florida Atlantic University
- Laboratory for Coordination Dynamics (http://www.ccs.fau.edu/html_old/coordlab.htm/) - Florida Atlantic University
- BM-Science (http://www.bm-science.com/) - Brain & Mind Technologies Research Centre, Finland
- An update on the global workspace theory (http://cogweb.ucla.edu/CogSci/Baars-update_03.html/) - article discussing the global workspace theory in the context of metastability in the brain.

Interactomics

Interactomics is a discipline at the intersection of bioinformatics and biology that deals with studying both the interactions and the consequences of those interactions between and among proteins, and other molecules within a cell[1] . The network of all such interactions is called the Interactome. Interactomics thus aims to compare such networks of interactions (i.e., interactomes) between and within species in order to find how the traits of such networks are either preserved or varied. From a mathematical, or → mathematical biology viewpoint an interactome network is a graph or a category representing the most important interactions pertinent to the normal physiological functions of a cell or organism.

Interactomics is an example of "top-down" systems biology, which takes an overhead, as well as overall, view of a biosystem or organism. Large sets of genome-wide and proteomic data are collected, and correlations between different molecules are inferred. From the data new hypotheses are formulated about feedbacks between these molecules. These hypotheses can then be tested by new experiments[2] .

Through the study of the interaction of all of the molecules in a cell the field looks to gain a deeper understanding of genome function and evolution than just examining an individual genome in isolation[1] . Interactomics goes beyond cellular proteomics in that it not only attempts to characterize the interaction between proteins, but between all molecules in the cell.

Methods of interactomics

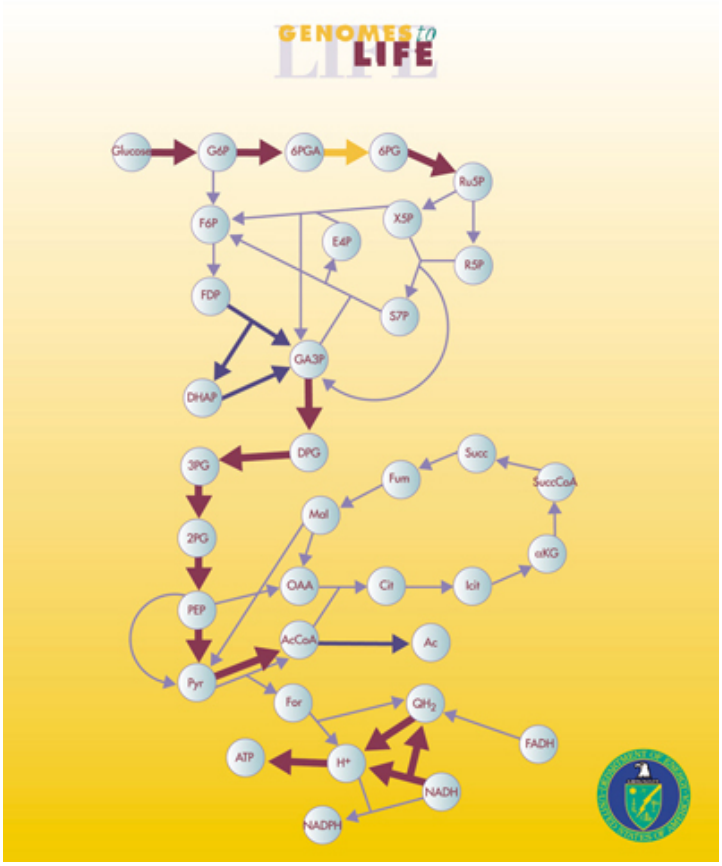
The study of the interactome requires the collection of large amounts of data by way of high throughput experiments. Through these experiments a large number of data points are collected from a single organism under a small number of perturbations[2] These experiments include:

- Two-hybrid screening
- Tandem Affinity Purification
- X-ray tomography
- Optical fluorescence microscopy

Recent developments

The field of interactomics is currently rapidly expanding and developing. While no biological interactomes have been fully characterized. Over 90% of proteins in *Saccharomyces cerevisiae* have been screened and their interactions characterized, making it the first interactome to be nearly fully specified [3] .

Also there have been recent systematic attempts to explore the human interactome[1] and [4] .



Metabolic Network Model for Escherichia coli.

Other species whose interactomes have been studied in some detail include *Caenorhabditis elegans* and *Drosophila melanogaster*.

Criticisms and concerns

Kiemer and Cesareni[1] raise the following concerns with the current state of the field:

- The experimental procedures associated with the field are error prone leading to "noisy results". This leads to 30% of all reported interactions being artifacts. In fact, two groups using the same techniques on the same organism found less than 30% interactions in common.
- Techniques may be biased, i.e. the technique determines which interactions are found.
- Ineractomes are not nearly complete with perhaps the exception of *S. cerivisiae*.
- While genomes are stable, interactomes may vary between tissues and developmental stages.

- Genomics compares amino acids, and nucleotides which are in a sense unchangeable, but interactomics compares proteins and other molecules which are subject to mutation and evolution.
- It is difficult to match evolutionarily related proteins in distantly related species.

See also

- Interaction network
- Proteomics
- Metabolic network
- Metabolic network modelling
- Metabolic pathway
- Genomics
- → Mathematical biology
- → Systems biology

References

[1] Kiemer, L; G Cesareni (2007). "Comparative interactomics: comparing apples and pears?". *TRENDS in Biochemistry* **25**: 448–454. doi: 10.1016/j.tibtech.2007.08.002 (http://dx.doi.org/10.1016/j.tibtech.2007.08.002).

[2] Bruggeman, F J; H V Westerhoff (2006). "The nature of systems biology". *TRENDS in Microbiology* **15**: 45–50. doi: 10.1016/j.tim.2006.11.003 (http://dx.doi.org/10.1016/j.tim.2006.11.003).

[3] Krogan, NJ; et al. (2006). "Global landscape of protein complexes in the yeast *Saccharomyeses Cerivisiae* ". *Nature* **440**: 637–643. doi: 10.1038/nature04670 (http://dx.doi.org/10.1038/nature04670).

[4] further citation needed

External links

- Interactomics.org (http://interactomics.org). A dedicated interactomics web site operated under BioLicense.
- Interactome.org (http://interactome.org). An interactome wiki site.
- PSIbase (http://psibase.kobic.re.kr) Structural Interactome Map of all Proteins.
- Omics.org (http://omics.org). An omics portal site that is openfree (under BioLicense)
- Genomics.org (http://genomics.org). A Genomics wiki site.
- Comparative Interactomics analysis of protein family interaction networks using PSIMAP (protein structural interactome map) (http://bioinformatics.oxfordjournals.org/cgi/content/full/21/15/3234)
- Interaction interfaces in proteins via the Voronoi diagram of atoms (http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6TYR-4KXVD30-2&_user=10&_coverDate=11/30/2006&_rdoc=1&_fmt=&_orig=search&_sort=d&view=c&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&md5=8361bf3fe7834b4642cdda3b979de8bb)
- Using convex hulls to extract interaction interfaces from known structures. Panos Dafas, Dan Bolser, Jacek Gomoluch, Jong Park, and Michael Schroeder. Bioinformatics 2004 20: 1486-1490.
- PSIbase: a database of Protein Structural Interactome map (PSIMAP). Sungsam Gong, Giseok Yoon, Insoo Jang Bioinformatics 2005.
- Mapping Protein Family Interactions : Intramolecular and Intermolecular Protein Family Interaction Repertoires in the PDB and Yeast, Jong Park, Michael Lappe & Sarah A.

Teichmann,J.M.B (2001).

- Semantic Systems Biology (http://www.semantic-systems-biology.org)

Article Sources and Contributors

Dynamic system *Source*: http://en.wikipedia.org/w/index.php?oldid=15907006 *Contributors*: -

Dynamical systems theory *Source*: http://en.wikipedia.org/w/index.php?oldid=292233393 *Contributors*: Arcfrk, Blaisorblade, Bscotland, Charles Matthews, Charvest, Delaszk, Elijahmeeks, Epbr123, Erkan Yilmaz, Giftlite, Jhaldenwang, Jyoshimi, Linas, Mdd, Quantoyster, Salix alba, Sviemeister, Tamtamar, XL2D, 33 anonymous edits

List of dynamical systems and differential equation topics *Source*: http://en.wikipedia.org/w/index.php?oldid=17634981 *Contributors*: -

Carathéodory's theorem (conformal mapping) *Source*: http://en.wikipedia.org/w/index.php?oldid=287284335 *Contributors*: Adam majewski, BeteNoir, Charles Matthews, DavidDumas, Gaius Cornelius, Giftlite, Linas, Michael Hardy, Pomte, Silverfish, Tosha, 2 anonymous edits

Dynamics of Markovian particles *Source*: http://en.wikipedia.org/w/index.php?oldid=275949632 *Contributors*: Bergner, Czolgolz, ERobson, Fabrictramp, Icairns, JPG-GR, Malcolma, Mbell, Oleg Alexandrov, ShakespeareFan00, 14 anonymous edits

Statistical physics *Source*: http://en.wikipedia.org/w/index.php?oldid=289763137 *Contributors*: 213.20.48.xxx, Abtract, Charles Matthews, Charvest, Conversion script, Cyan, Da Joe, Djr32, Eaefremov, Gjd001, Headbomb, Icairns, Jheald, Jimmaths, Kar.ma, Karol Langner, Moink, Mpatel, Noeckel, Numbo3, Omnipedian, Physicistjedi, SamuelRiv, Synergy, The Anome, TimBentley, Wam junkie, Woahtoster, XJamRastafire, 13 anonymous edits

Statistical mechanics *Source*: http://en.wikipedia.org/w/index.php?oldid=294155089 *Contributors*: APH, Abtract, Aleksas, Alison, Ancheta Wis, Andries, Anoko moonlight, Ap, Boardhead, Bogdangiusca, Brews ohare, Brianjd, Bryan Derksen, BryanD, Charles Matthews, Charvest, Chrisch, Complexica, Conversion script, Cordell, DMTagatac, Dancter, Daniel5127, Davennmarr, David Woolley, Den fjättrade ankan, DiceDiceBaby, Djr32, Djus, Doprendek, Edgar181, Edkarpov, Edsanville, Elwikipedista, Eman, Fephisto, Frokor, G716, Gail, GangofOne, Giftlite, Gurch, HappyCamper, Ht686rg90, Isopropyl, IvanLanin, JabberWok, Jheald, John Palkovic, Jorgenumata, Karl-Henner, Karol Langner, Kzollman, Lantonov, LeadSongDog, Linas, Linuxlad, Locke9k, Loupeter, Lyonspen, MK8, Mary blackwell, Mct mht, Michael Hardy, Michael L. Kaufman, Miguel, Mikez, Mlys, Monedula, Moondarkx, Mpatel, Mxn, Nitya Dharma, Nnh, P99am, PAR, Patrick, Peabeejay, Perelaar, Peterlin, Phudga, Phys, PhysPhD, Politepunk, Radagast83, RandomP, Rjwilmsi, Ryanmcdaniel, SDC, Sadi Carnot, Samkung, Scorwin, Sheliak, SimpsonDG, Steve Omohundro, StewartMH, StradivariusTV, Template namespace initialisation script, That Guy, From That Show!, The Anome, The Cunctator, The Original Wildbear, The.orpheus, Thingg, ThorinMuglindir, Tim Starling, TravisAF, Truthnlove, Van helsing, Vql, Wavelength, Weiguxp, Wiki me, Xp54321, Yevgeny Kats, Yill577, 114 anonymous edits

Molecular dynamics *Source*: http://en.wikipedia.org/w/index.php?oldid=293834896 *Contributors*: Agilemolecule, Alex.g, Amire80, Ammatsun, Anthracene, Anxdo, ApJilly, Astavats, Ayucat, Bbullot, Bduke, BenFrantzDale, Bubba hotep, Chris the speller, Cortonin, Cwassman, DMacks, DRider, Dacb, DeadEyeArrow, Demus Wiesbaden, Dicklyon, Dietmar.paschek, DragonflySixtyseven, Drswenson, Ebuchol, Ehdr, Gentgeen, Giftlite, Huckit, Itamblyn, Itub, JWSchmidt, Jerome Charles Potts, Jorgenumata, Jugander, Kaihsu, Karol Langner, Katherine Folsom, Kennylam, Kevyn, Kjaergaard, Knordlun, Laurent1979, Lexor, LiDaobing, Linas, Lomenoldur, Ludx, Maduixa, Marchuta, Marx Gomes, Mateusz Galuszka, Mattopia, Md Arshad Iqbal, Mihoopes, Mr Marie Weaver, Msuzen, Nicolasbock, Oiramrasec, Opabinia regalis, Ossi, P99am, Paul.raymond.brenner, Pedrito, Pelister, PhCOOH, Pksach, PrometheusX303, Raviwiki4, Rob Hooft, Roo1812, Sandycx, Shura58, Smoe, Smremde, Stewartadcock, Sudiarta, TStein, Themfromspace, Thorwald, Utcursch, Van helsing, Whanrott, Wikimcmd, Wittgenstein77, Wiz9999, Xavier andrade, Yrtgm, 198 anonymous edits

Molecular modelling *Source*: http://en.wikipedia.org/w/index.php?oldid=293943983 *Contributors*: ACBest, Agilemolecule, Akpakp, Amalas, Anonymi, Anotherdendron, Bbullot, Bduke, BenFrantzDale, Bensaccount, Bikadi, Billgunn, Bio-ITWorld, Biophys, BokicaK, Bspahh, Cacycle, Chenmengen, DMacks, DeadEyeArrow, Dicklyon, Drmolecule, Edguy99, ElaineMeng, Enric Naval, Gaius Cornelius, Gogo Dodo, Graik, Hu, Hu12, Huyie, Icairns, Itub, JaGa, Jamitzky, Jason Quinn, Joerg Kurt Wegner, Karol Langner, Kazkaskazkasako, Keilana, Lantonov, Lexor, LiDaobing, Ms2ger, Nicolazonta, Nono64, Nubiatech, Ohlinger, Ohnoitsjamie, P99am, Para, Petermr, Pieter Kuiper, ProteusCoop, Puppy8800, Rich Farmbrough, Richard Arthur Norton (1958-), Shura58, SimonTrew, Some standardized rigour, Splette, TheParanoidOne, Transisto, Trevyn, Unconcerned, Utcursch, Uvainio, Valeryns, Van helsing, Vriend, Weiguxp, Wikimcmd, Xebvor, YAYsocialism, Zmm, 104 anonymous edits

Monte Carlo method *Source*: http://en.wikipedia.org/w/index.php?oldid=292356102 *Contributors*: *drew, ABCD, Aardvark92, Adfred123, Aferistas, Agilemolecule, Akanksh, Alanbly, Albmont, AlexBIOSS, AlexandreCam, AlfredR, Alliance09, Altenmann, Andrea Parri, Andreas Kaufmann, Angelbo, Aniu, Apanag, Aspuru, Atlant, Avalcarce, Aznrocket, BAxelrod, BConleyEEPE, Banano03, Banus, Bduke, BenFrantzDale, BenTrotsky, Bender235, Bensaccount, BillGosset, Bkell, Blotwell, Bmaddy, Bobo192, Boffob, Boredzo, Broquaint, Btyner, CRGreathouse, Caiaffa, Charles Matthews, ChicagoActuary, Cibergili, Cm the p, Colonies Chris, Coneslayer, Cretog8, Criter, Cybercobra, Cython1, DMG413, Damistmu, Ddcampayo, Ddxc, Digemedi, Ds53, Duck ears, Duncharris, Dylanwhs, ERosa, EldKatt, Elpincha, Elwikipedista, Eudaemonic3, Ezrakilty, Fastfission, Fintor, Flammifer, Frozen fish, Furrykef, G716, Giftlite, Gilliam, Goudzovski, GraemeL, GrayCalhoun, Greenyoda, Grestrepo, Gtrmp, Gökhan, Hanksname, Hawaiian717, Hokanomono, Hu12, Hubbardaie, ILikeThings, IanOsgood, Inrad, Itub, Jackal irl, Janpedia, JavaManAz, Jeffq, Jitse Niesen, Joey0084, JohnOwens, Jorgenumata, Jsarratt, Jugander, Jérôme, K.lee, KSmrq, KaHa242, Karol Langner, Kenmckinley, Kimys, Knordlun, Kroese, Kummi, Kuru, Lambyte, LeoTrottier, Levin, Lexor, LoveMonkey, Malatesta, Male1979, ManchotPi, Marcofalcioni, Martinp, Masatran, Mathcount, MaxHD, Maxentrope, Maylene, Melcombe, Michael Hardy, Mikael V, Misha Stepanov, Mnath, Moink, Mtford, Nagasaka, Nanshu, Narayanese, Nelson50, Nosophorus, Nsaa, Nuno Tavares, Nvartaniucsd, Ohnoitsjamie, Oli Filth, Oneboy, Orderud, OrgasGirl, P99am, Paul August, PaulxSA, Pbroks13, Pcb21, Pete.Hurd, PeterBoun, Pgreenfinch, Philopp, Pibwl, Pinguin.tk, PlantTrees, Pne, Popsracer, Poupoune5, Qadro, Quantumelfmage, Quentar, Qxz, RWillwerth, Ramin Nakisa, Redgolpe, Renesis, Richie Rocks, Rinconsoleao, Rjmccall, Ronnotel, Rs2, SKelly1313, Sam Korn, Samratvishaljain, Sergio.ballestrero, Shreevatsa, Snoyes, Somewherepurple, Spellmaster, Splash6, SpuriousQ, Stefanez, Stefanomione, StewartMH, Stimpy, Storm Rider, Superninja, Tarantola, Taxman, Tayste, Tesi1700, Theron110, Tiger Khan, Tim Starling, Tom harrison, Tooksteps, Trebor, Twooars, Urdutext, Vipuser, VoseSoftware, Wile E. Heresiarch, Yoderj, Zarniwoot, Zoicon5, Zr40, Zuidervled, 307 anonymous edits

Monte Carlo molecular modeling *Source*: http://en.wikipedia.org/w/index.php?oldid=275099259 *Contributors*: Agilemolecule, Alternativereactionpathway, BenFrantzDale, D-rew, Ddcampayo, Guslacerda, Itub, Karol Langner, MaxHD, Michael Hardy, 2 anonymous edits

Monte Carlo integration *Source*: http://en.wikipedia.org/w/index.php?oldid=288690468 *Contributors*: Aaron Rotenberg, AlphaPyro, Bakken, Berland, BigJohnHenry, Boffob, Chrispounds, Dreftymac, Dzordzm, Ekjon Lok, Fintor, Frau Holle, Giftlite, Gmelfi, Jitse Niesen, Jlpinar83, Melcombe, Robert Samal, Shanth phy, Shreevatsa, Spudbeach, Yoderj, 22 anonymous edits

Quasi-Monte Carlo method *Source*: http://en.wikipedia.org/w/index.php?oldid=193301801 *Contributors*: Albmont, Charles Matthews, Jitse Niesen, Karol Langner, Klaus scheicher, Ntmatter, Pcb21, Ruud Koot, Stefanomione, Wile E. Heresiarch, 8 anonymous edits

Quantum thermodynamics *Source*: http://en.wikipedia.org/w/index.php?oldid=270793573 *Contributors*: Boardhead, Djr32, Leiutenant Yung Sam Kim, Michael C Price, Rich257, Sadi Carnot, Sholto Maud, Srleffler, Togo, Voorlandt, 2 anonymous edits

Quantum chemistry *Source*: http://en.wikipedia.org/w/index.php?oldid=292520271 *Contributors*: 144.189.40.xxx, 208.40.185.xxx, 4lex, Acroterion, Alansohn, Ayla, BTDenyer, Bci2, Bduke, Bob, BrianY, Bubbha, CDN99, Capecodeph, ChemGardener, CloudNine, Cmdrjameson, CommonsDelinker, Conversion script, Cool3, Cypa, EdJohnston, Edsanville, EmilyT, Euryalus, Gentgeen, Gershom, Giftlite, Glenn, GregorB, Haljolad, HappyCamper, Holdran, Hugo-cs, Ian Pitchford, Itub, James 007, Jantop, JerrySteal, Kaliumfredrik, Karol Langner, Keenan Pepper, Keilana, Koinut, Krash, La goutte de pluie, Lampuchi, Ligulem, Lijuni, Looxix, M stone, Martin Hedegaard, Meisfunny, Milo, Nickptar, Noisy, Nzzl, Okedem, Perelaar, Ratol, Rifleman 82, SHL-at-Sv, SQL, Sadi Carnot, Salsb, Shalom Yechiel, Shanel, Sidhekin, Smoe, Sunev, Tasudrty, Terhorstj, Timwi, UninvitedCompany, Vb, Vgy7ujm, Vig vimarsh, Voigfdsa, Vsmith, W.F.Galway, Wiki alf, Yurik, Zarniwoot, Zeimusu, Александър, عالم بوبجم, 132 anonymous edits

Quantum Monte Carlo *Source*: http://en.wikipedia.org/w/index.php?oldid=294437097 *Contributors*: Acipsen, Amyoungil, Bci2, Conscious, Henry Delforn, Isilanes, Jheriko, Karol Langner, Lucaskw, Mdt26a, Melcombe, Michael Hardy, NNemec, Pablomme, Paulcardan, Rbonvall, Rich Farmbrough, Rjwilmsi, Sagaciousuk, Supersion77, TestPilot, Trigger hippie77, UkPaolo, Veinor, Vgy7ujm, Vyznev Xnebara, WilliamDParker, Wirawan0, 37 anonymous edits

Force field *Source*: http://en.wikipedia.org/w/index.php?oldid=292605297 *Contributors*: Anakin101, Ausir, Boothferry, Cburnett, DarkHorizon, Decktiledirect, Dockingman, Edcolins, Gene Nygaard, Holding Ray, Jiy, Kaihsu, Karol Langner, Kchishol1970, Kellen`, LiDaobing, Marj Tiefert, Marzillius, MegX, Michael Hardy, Mrwojo, Notebook85, Oleg Alexandrov, Petergans, Phoolan2000, Pion, Podcaster, Robert Fraser, Sukael, TheOtherJesse, Trevyn, Vicki Rosenzweig, Vincent kraeutler, 50 anonymous edits

Jahn-Teller *Source*: http://en.wikipedia.org/w/index.php?oldid=236798312 *Contributors*: -

Computational Science *Source*: http://en.wikipedia.org/w/index.php?oldid=174883659 *Contributors*: -

Computational Chemistry List *Source*: http://en.wikipedia.org/w/index.php?oldid=114162327 *Contributors*: Bduke, Bwpach, Elonka, Rich Farmbrough, Utcursch, 1 anonymous edits

Mathematical model *Source*: http://en.wikipedia.org/w/index.php?oldid=291597966 *Contributors*: Abdull, Abdullais4u, Abune, Agor153, Altenmann, Arvindn, Atlant, Audriusa, Binarypower, Brianjd, CarlHewitt, Carlodn6, Cazort, Conversion script, Cybercobra, Dakart, Derek Ross, Dori, Drini, Dterp, Dvsphanindra, Dysprosia, Elapsed, EmersonLowry, Emperorbma, Eurosong, Farazgiki, Filippof, Fioravante Patrone en, Frau Holle, G.de.Lange, GiantSloth, Giftlite, Globalsolidarity, Gogo Dodo, Goodralph, Gregbard, Grubber, Hans Adler, Hede2000, Helix84, Henrygb, HolgerK, Hxxvxxy, Hydrargyrum, JRSpriggs, JWSchmidt, Jdpipe, John Deas, JohnOwens, Jonnat, Josephfrodo, Karnesky, Kbdank71, Kingturtle, Lexor, MCrawford, Maedin, Maksim-e, Marek69, Martin451, MathMartin, Matqkks, Mayooranathan, Mdd, Meemee878, Michael Hardy, Millancad, MrOllie, Msh210, Neilc, Nikai, Nshackles, Obradovic Goran, Oleg Alexandrov, Oliver Lineham, Olivier, Omicronpersei8, PMDrive1061, Paolo.dL, Passw0rd, Pdenapo, Phanerozoic, Porcher, Queenie, Rbakker99, RoyBoy, Sam Douglas, Sangwinc, Silverhelm, Sjö, Skbkekas, Smmurphy, Soy ivan, Spiritia, Spradlig, Squidonius, T.ogar, Tasudrty, Tbackstr, Tbsmith, The Anome, Tilin, TittoAssini, Tom Fararo, Tomas e, Tparameter, Trebor, Trovatore, Vina, Vlado0605, Wavehunter, Wavelength, Wesley, Winhunter, Wsiegmund, Yotaloop, 138 anonymous edits

Mathematical chemistry *Source*: http://en.wikipedia.org/w/index.php?oldid=294429148 *Contributors*: Altenmann, Baz.77.243.99.32, DMacks, Giftlite, Hamleteer, Itub, Linas, Maxal, Niksab, Remuel, Tim32, 10 anonymous edits

Molecular graphics *Source*: http://en.wikipedia.org/w/index.php?oldid=285442351 *Contributors*: ALoopingIcon, Agilemolecule, Altenmann, Arch dude, Chemistrannik, Chenmengen, CzarB, Dcrjsr, Dreftymac, Edguy99, Edward, EranHodis, Fvasconcellos, Harryboyles, Icep, JLSussman, Jweiss11, Karol Langner, Linforest, McVities, Mdd, Mobius, Mrug2, NapoliRoma, NicoV, Ohnoitsjamie, Outriggr, P99am, PBarak, Petermr, ProveIt, Rjwilmsi, Rogerb67, SchuminWeb, Shura58, Sjoerd de Vries, SkyWalker, Thumperward, Timrollpickering, Vriend, Walkerma, 16 anonymous edits

Complex dynamics *Source*: http://en.wikipedia.org/w/index.php?oldid=252015761 *Contributors*: Adam majewski, Antariki Vandanamu, Charles Matthews, El C, Gscshoyru, Icairns, Monobi, Ntmatter, Oleg Alexandrov, Pt, Silverfish, 3 anonymous edits

Topological dynamics *Source*: http://en.wikipedia.org/w/index.php?oldid=285184911 *Contributors*: Arcfrk, Charvest, Michael Hardy, SiamakT

Topological conjugacy *Source*: http://en.wikipedia.org/w/index.php?oldid=292568705 *Contributors*: Adam majewski, Bci2, Charles Matthews, Charvest, Dvavasour, Linas, Michael Hardy, Rjwilmsi, SiegeLord, 1 anonymous edits

Network dynamics *Source*: http://en.wikipedia.org/w/index.php?oldid=214605473 *Contributors*: Delaszk

Dynamic network analysis *Source*: http://en.wikipedia.org/w/index.php?oldid=290968141 *Contributors*: 477TataB, AZK, AbsolutDan, Argon233, Beetstra, Delaszk, Diabloblue, Douglas R. White, Erkan Yilmaz, JonHarder, Mattdereno, Melcombe, Michael Hardy, Mind123, Porqin, SiobhanHansa, Supernet, Supertabular, Terrillfrantz, Wikidemon, Yassens, 14 anonymous edits

Theoretical biology *Source*: http://en.wikipedia.org/w/index.php?oldid=292513287 *Contributors*: Alamowit, Alan Liefting, Bci2, Boninho, Boresal, Cacycle, Cazort, Den fjättrade ankan, Dj Capricorn, Doctorage, Eliezg, G716, Guettarda, Hans Adler, Hydro2, Jeff3000, Jrf, Jwdietrich2, Kakugo, Lexor, Lquilter, Marashie, Marsian, Maurreen, Mdd, Occhanikov, Oldekop, PhDP, Pietrosperoni, Porcher, Ruud Koot, Tassedethe, Tompw, Txomin, WebDrake, WilliamBonfieldFRS, 24 anonymous edits

Mathematical biology *Source*: http://en.wikipedia.org/w/index.php?oldid=293117766 *Contributors*: Adoniscik, Agilemolecule, Agricola44, Alan Liefting, Anclation, Andreas td, Aua, Audriusa, Bci2, Bduke, Berland, BillWSmithJr, Ceyockey, Charvest, Chopchopwhitey, Commander Nemet, Constructive editor, Cquan, Den fjättrade ankan, Durova, Dysprosia, Eduardoporcher, Fredrik, Gandalfxviv, Geronimo20, Guettarda, Henriok, Honeydew, Imoen, Jag123, Jaibe, Jennavecia, JonHarder, Jonsafari, Jpbowen, Jwdietrich2, Karl-Henner, Kripkenstein, Leptictidium, Lexor, Lquilter, M stone, MATThematical, Malcolm Farmer, Mathmoclaire, Maurreen, Melcombe, Michael Hardy, Oldekop, Oli Filth, Open4D, Owlmonkey, Percy Snoodle, PeterStJohn, PhDP, Plw, Porcher, Rich Farmbrough, Sintaku, Sir hubert, Squidonius, Ssavelan, StN, Stemonitis, Tompw, Triwbe, Vina, Wavelength, 68 anonymous edits

Systems biology *Source*: http://en.wikipedia.org/w/index.php?oldid=294364649 *Contributors*: APH, Aciel, Alan Liefting, AlirezaShaneh, Amandadawnbesemer, Amirsnik, Andreas td, Arthena, Asadrahman, Aua, Bad Cat, Bamess, BatteryIncluded, Bci2, Bio-ITWorld, Biochaos, Biophysik, Blueleezard, Boku wa kage, Broadbeer, CRGreathouse, CX, Can't sleep, clown will eat me, Captain-tucker, Ceolas, Charlenelieu, CharonZ, Ckatz, Claronow, ColinGillespie, Cquan, Crodriguel, D6, DanielNuyu, Delta Xi, Dmb000006, Drgarden, Droyarzun, Duelist135, Edaddison, Edward, Electric sheep, Erick.Antezana, Erkan Yilmaz, Eveillar, FLeader, Fences and windows, Fenice, Fletcher04, Foggy29, Fredrik, Garychurchill, Gcm, Gdrahnier, Ggonnell, Giftlite, Gwolfe, Heisner, HexiToFor, IPSOS, JRSocInterface, JaGa, Jdegreef, Jethero, Jondel, Jongbhak, Jpbowen, JulioVeraGon, Jwdietrich2, Kane5187, Karthik.raman, Kcordina, KirbyRandolf, Kku, Klenod, Klipkow, Lauranrg, Lenov, Letranova, Lexor, Lilia Alberghina, Linkman21, Lkathmann, Massbiotech, Mdd, Michael Fourman, Michael Hardy, Miguel Andrade, MikeHucka, Mkotl, Mkuiper, Mmxx, Mobashirgenome, Molelect, N2e, NBeale, NIH Media, Natelewis, Nbaliga, Neilbeach, Nemenman, Netsnipe, Nick Green, O RLY?, Ombudsman, Opertinicy, Patho, PaulGarner, Pkahlem, Pvosta, Quarl, Rajah, Reggiebird, Rich Farmbrough, Rjwilmsi, Robnpov, Rvencio, Rwcitek, Satish.vammi, SeeGee, Senu, Seuss01, Sholto Maud, Srlasky, Steinsky, Stewartadcock, Synthetic Biologist, Tagishsimon, Template namespace initialisation script, Thorwald, Triamus, Unauthorised Immunophysicist, Vangos, Versus22, Vonkje, WLU, Waltpohl, Wavelength, Whosasking, Xeaa, Zargulon, Zlite, Zoicon5, عیسی, 350 anonymous edits

DNA Dynamics *Source*: http://en.wikipedia.org/w/index.php?oldid=294104535 *Contributors*: Bci2, Chris the speller, CommonsDelinker, Ironholds, Potatoswatter

Metastability in the brain *Source*: http://en.wikipedia.org/w/index.php?oldid=270840418 *Contributors*: Arthur Rubin, CosineKitty, East718, Fnielsen, Grumpyyoungman01, Jfdwolff, Mainstream Nerd, Mdude85, Mysid, Oldgrannyshoes, Pearle, RichardVeryard, Zoz, 18 anonymous edits

Interactomics *Source*: http://en.wikipedia.org/w/index.php?oldid=293358442 *Contributors*: Bci2, Bdevrees, Erick.Antezana, Erodium, Jong, Jongbhak, Karthik.raman, Lexor, Llull, Niteowlneils, PDH, Pekaje, Rajah, Tucsontt, 8 anonymous edits

Image Sources, Licenses and Contributors

Image:Lorenz attractor yb.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Lorenz_attractor_yb.svg *License*: Creative Commons Attribution-Sharealike 2.5 *Contributors*: User:Dschwen, User:Wikimol

Image:Erays.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Erays.png *License*: unknown *Contributors*: User:Adam majewski

Image:Mdalgorithm.PNG *Source*: http://en.wikipedia.org/w/index.php?title=File:Mdalgorithm.PNG *License*: Public Domain *Contributors*: User:Knordlun

Image:peptide angles.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Peptide_angles.png *License*: unknown *Contributors*: User:Bensaccount

Image:Hardware-accelerated-molecular-modeling.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Hardware-accelerated-molecular-modeling.png *License*: Public Domain *Contributors*: User:P99am

Image:Monte carlo method.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Monte_carlo_method.svg *License*: Public Domain *Contributors*: --pbroks13talk? Original uploader was Pbroks13 at en.wikipedia

Image:MonteCarloIntegrationCircle.png *Source*: http://en.wikipedia.org/w/index.php?title=File:MonteCarloIntegrationCircle.png *License*: Public Domain *Contributors*: User:Yoderj

Image:Strata.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Strata.png *License*: unknown *Contributors*: User:Bakken

Image:jmol1.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Jmol1.png *License*: unknown *Contributors*: Peter Murray-Rust

Image:Hemagglutinin molecule.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Hemagglutinin_molecule.png *License*: GNU Free Documentation License *Contributors*: U.S. National Institutes of Health.

Image:FormicAcid.pdb.png *Source*: http://en.wikipedia.org/w/index.php?title=File:FormicAcid.pdb.png *License*: Public Domain *Contributors*: Csörföly D, Cwbm (commons)

Image:Isosurface on molecule.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Isosurface_on_molecule.jpg *License*: unknown *Contributors*: StoatBringer

Image:porin.qutemol.dl.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Porin.qutemol.dl.png *License*: unknown *Contributors*: ALoopingIcon

Image:porin.qutemol.ao.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Porin.qutemol.ao.png *License*: unknown *Contributors*: ALoopingIcon

Image:JmolStick.PNG *Source*: http://en.wikipedia.org/w/index.php?title=File:JmolStick.PNG *License*: unknown *Contributors*: Peter Murray-Rust

Image:DynamicNetworkAnalysisExample.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:DynamicNetworkAnalysisExample.jpg *License*: Public Domain *Contributors*: Terrillfrantz

Image:Cell cycle bifurcation diagram.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Cell_cycle_bifurcation_diagram.jpg *License*: unknown *Contributors*: User:Squidonius

Image:Genomics GTL Pictorial Program.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Genomics_GTL_Pictorial_Program.jpg *License*: Public Domain *Contributors*: Mdd

Image:Signal transduction v1.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Signal_transduction_v1.png *License*: GNU Free Documentation License *Contributors*: Original uploader was Roadnottaken at en.wikipedia

File:DNA-fragment-3D-vdW.png *Source*: http://en.wikipedia.org/w/index.php?title=File:DNA-fragment-3D-vdW.png *License*: Public Domain *Contributors*: Benjah-bmm27

File:ADN animation.gif *Source*: http://en.wikipedia.org/w/index.php?title=File:ADN_animation.gif *License*: Public Domain *Contributors*: Aushulz, Bawolff, Brian0918, Kersti Nebelsiek, Magadan, Mattes, Origamiemensch, Stevenfruitsmaak, 3 anonymous edits

File:Simple harmonic oscillator.gif *Source*: http://en.wikipedia.org/w/index.php?title=File:Simple_harmonic_oscillator.gif *License*: Public Domain *Contributors*: User:Oleg Alexandrov

File:A-DNA orbit animated small.gif *Source*: http://en.wikipedia.org/w/index.php?title=File:A-DNA_orbit_animated_small.gif *License*: GNU Free Documentation License *Contributors*: User:Bstlee, User:Zephyris

File:3D model hydrogen bonds in water.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:3D_model_hydrogen_bonds_in_water.jpg *License*: GNU Free Documentation License *Contributors*: User:snek01

File:DNA labels.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:DNA_labels.jpg *License*: GNU Free Documentation License *Contributors*: User:Raul654

File:A-B-Z-DNA Side View.png *Source*: http://en.wikipedia.org/w/index.php?title=File:A-B-Z-DNA_Side_View.png *License*: Public Domain *Contributors*: Original uploader was Thorwald at en.wikipedia

File:ABDNAxrgpj.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:ABDNAxrgpj.jpg *License*: GNU Free Documentation License *Contributors*: I.C. Baianu et al.

File:BU Bio5.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:BU_Bio5.jpg *License*: Creative Commons Attribution-Sharealike 2.0 *Contributors*: Original uploader was Elapied at fr.wikipedia

File:Parallel telomere quadruple.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Parallel_telomere_quadruple.png *License*: unknown *Contributors*: User:Splette

File:Four-way DNA junction.gif *Source*: http://en.wikipedia.org/w/index.php?title=File:Four-way_DNA_junction.gif *License*: Public Domain *Contributors*: Aushulz, Molatwork, Origamiemensch, TimVickers, 1 anonymous edits

File:Sarfus.DNABiochip.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Sarfus.DNABiochip.jpg *License*: unknown *Contributors*: Nanolane

File:DNA nanostructures.png *Source*: http://en.wikipedia.org/w/index.php?title=File:DNA_nanostructures.png *License*: unknown *Contributors*: (Images were kindly provided by Thomas H. LaBean and Hao Yan.)

File:Circular DNA Supercoiling.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Circular_DNA_Supercoiling.png *License*: GNU Free Documentation License *Contributors*: Richard Wheeler (Zephyris)

File:Rothemund-DNA-SierpinskiGasket.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Rothemund-DNA-SierpinskiGasket.jpg *License*: Creative Commons Attribution 2.5 *Contributors*: Antony-22

File:RNA pol.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:RNA_pol.jpg *License*: Public Domain *Contributors*: InfoCan

File:Primase 3B39.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Primase_3B39.png *License*: Public Domain *Contributors*: own work

File:MGMT+DNA 1T38.png *Source*: http://en.wikipedia.org/w/index.php?title=File:MGMT+DNA_1T38.png *License*: Public Domain *Contributors*: own work

File:DNA damaged by carcinogenic 2-aminofluorene AF .jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:DNA_damaged_by_carcinogenic_2-aminofluorene_AF_.jpg *License*: Public Domain *Contributors*: Brian E. Hingerty, Oak Ridge National Laboratory Suse Broyde, New York University Dinshaw J. Patel, Memorial Sloan Kettering Cancer Center

File:Chr2 orang human.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Chr2_orang_human.jpg *License*: Creative Commons Attribution-Sharealike 2.5 *Contributors*: Verena Schubel, Stefan Müller, Department Biologie der Ludwig-Maximilians-Universität München.

File:Plasmid emNL.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Plasmid_emNL.jpg *License*: GNU Free Documentation License *Contributors*: Denniss, Glenn, Rasbak

File:3D-SIM-3 Prophase 3 color.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:3D-SIM-3_Prophase_3_color.jpg *License*: Creative Commons Attribution-Sharealike 3.0 *Contributors*: Lothar Schermelleh

File:Chromosome2 merge.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Chromosome2_merge.png *License*: Public Domain *Contributors*: Original uploader was Evercat at en.wikipedia

File:Chromosome Conformation Capture Technology.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Chromosome_Conformation_Capture_Technology.jpg *License*: Public Domain *Contributors*: User:Kangyun1985

File:PCR.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:PCR.svg *License*: unknown *Contributors*: User:Madprime

File:Pcr gel.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Pcr_gel.png *License*: GNU Free Documentation License *Contributors*: Habj, Ies, PatríciaR, Retama, Saperaud

File:SFP discovery principle.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:SFP_discovery_principle.jpg *License*: unknown *Contributors*: User:Agbiotec

File:Cdnaarray.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Cdnaarray.jpg *License*: unknown *Contributors*: Mangapoco

File:Expression of Human Wild-Type and P239S Mutant Palladin.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Expression_of_Human_Wild-Type_and_P239S_Mutant_Palladin.png *License*: unknown *Contributors*: see above

File:Plos VHL.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Plos_VHL.jpg *License*: Creative Commons Attribution 2.5 *Contributors*: Akinom, Anniolek, Filip em, Thommiddleton

File:Random genetic drift chart.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Random_genetic_drift_chart.png *License*: unknown *Contributors*: User:Professor marginalia

File:Signal transduction v1.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Signal_transduction_v1.png *License*: GNU Free Documentation License *Contributors*: Original uploader was Roadnottaken at en.wikipedia

File:Genomics GTL Pictorial Program.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Genomics_GTL_Pictorial_Program.jpg *License*: Public Domain *Contributors*: Mdd

File:Maldi informatics figure 6.JPG *Source*: http://en.wikipedia.org/w/index.php?title=File:Maldi_informatics_figure_6.JPG *License*: Public Domain *Contributors*: Rbeavis

File:Stokes shift.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Stokes_shift.png *License*: unknown *Contributors*: User:Mykhal

File:CARS Scheme.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:CARS_Scheme.svg *License*: unknown *Contributors*: Onno Gabriel

File:HyperspectralCube.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:HyperspectralCube.jpg *License*: Public Domain *Contributors*: Dr. Nicholas M. Short, Sr.

File:MultispectralComparedToHyperspectral.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:MultispectralComparedToHyperspectral.jpg *License*: Public Domain *Contributors*: Dr. Nicholas M. Short, Sr.

File:Tirfm.svg *Source*: http://en.wikipedia.org/w/index.php?title=File:Tirfm.svg *License*: Public Domain *Contributors*: Dawid Kulik

File:Fluorescence microscop.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Fluorescence_microscop.jpg *License*: unknown *Contributors*: Masur

File:Microscope And Digital Camera.JPG *Source*: http://en.wikipedia.org/w/index.php?title=File:Microscope_And_Digital_Camera.JPG *License*: GNU Free Documentation License *Contributors*: User:Zephyris

File:FluorescentCells.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:FluorescentCells.jpg *License*: Public Domain *Contributors*: DO11.10, Emijrp, NEON ja, Origamiemensch, Splette, Tolanor, 5 anonymous edits

File:Yeast membrane proteins.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Yeast_membrane_proteins.jpg *License*: unknown *Contributors*: User:Masur

File:S cerevisiae septins.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:S_cerevisiae_septins.jpg *License*: Public Domain *Contributors*: Spitfire ch, Philippsen Lab, Biozentrum Basel

File:Dividing Cell Fluorescence.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Dividing_Cell_Fluorescence.jpg *License*: unknown *Contributors*: Will-moore-dundee

File:HeLa Hoechst 33258.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:HeLa_Hoechst_33258.jpg *License*: Public Domain *Contributors*: TenOfAllTrades

File:FISH 13 21.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:FISH_13_21.jpg *License*: Public Domain *Contributors*: Gregor1976

File:Bloodcell sun flares pathology.jpeg *Source*: http://en.wikipedia.org/w/index.php?title=File:Bloodcell_sun_flares_pathology.jpeg *License*: Public Domain *Contributors*: Birindand, Karelj, NEON ja, 1 anonymous edits

File:Carboxysome 3 images.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Carboxysome_3_images.png *License*: Creative Commons Attribution 3.0 *Contributors*: Prof. Todd O. Yeates, UCLA Dept. of Chem. and Biochem.

File:DNA_nanostructures.png *Source*: http://en.wikipedia.org/w/index.php?title=File:DNA_nanostructures.png *License*: unknown *Contributors*: (Images were kindly provided by Thomas H. LaBean and Hao Yan.)

File:Holliday junction coloured.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Holliday_junction_coloured.png *License*: GNU Free Documentation License *Contributors*: Original uploader was Zephyris at en.wikipedia

File:Holliday Junction cropped.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Holliday_Junction_cropped.png *License*: GNU Free Documentation License *Contributors*: Original uploader was TimVickers at en.wikipedia

File:Atomic force microscope by Zureks.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Atomic_force_microscope_by_Zureks.jpg *License*: unknown *Contributors*: User:Zureks

File:Atomic force microscope block diagram.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Atomic_force_microscope_block_diagram.png *License*: Public Domain *Contributors*: Original uploader was Askewmind at en.wikipedia

File:AFM view of sodium chloride.gif *Source*: http://en.wikipedia.org/w/index.php?title=File:AFM_view_of_sodium_chloride.gif *License*: Public Domain *Contributors*: Courtesy of prof. Ernst Meyer, university of Basel

File:Single-Molecule-Under-Water-AFM-Tapping-Mode.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Single-Molecule-Under-Water-AFM-Tapping-Mode.jpg *License*: unknown *Contributors*: User:Yurko

Image:Self-Organization in Brain Fig1.png *Source*: http://en.wikipedia.org/w/index.php?title=File:Self-Organization_in_Brain_Fig1.png *License*: GNU Free Documentation License *Contributors*: Mdude85

Image:Metabolic Network Model for Escherichia coli.jpg *Source*: http://en.wikipedia.org/w/index.php?title=File:Metabolic_Network_Model_for_Escherichia_coli.jpg *License*: Public Domain *Contributors*: Mdd

License

Version 1.2, November 2002

0.PREAMBLE

The purpose of this License is to make a manual, textbook, or other functional and useful document "free" in the sense of freedom: to assure everyone the effective freedom to copy and redistribute it, with or without modifying it, either commercially or noncommercially. Secondarily, this License preserves for the author and publisher a way to get credit for their work, while not being considered responsible for modifications made by others.
This License is a kind of "copyleft", which means that derivative works of the document must themselves be free in the same sense. It complements the GNU General Public License, which is a copyleft license designed for free software.
We have designed this License in order to use it for manuals for free software, because free software needs free documentation: a free program should come with manuals providing the same freedoms that the software does. But this License is not limited to software manuals; it can be used for any textual work, regardless of subject matter or whether it is published as a printed book. We recommend this License principally for works whose purpose is instruction or reference.

1.APPLICABILITY AND DEFINITIONS

This License applies to any manual or other work, in any medium, that contains a notice placed by the copyright holder saying it can be distributed under the terms of this License. Such a notice grants a world-wide, royalty-free license, unlimited in duration, to use that work under the conditions stated herein. The "Document", below, refers to any such manual or work. Any member of the public is a licensee, and is addressed as "you". You accept the license if you copy, modify or distribute the work in a way requiring permission under copyright law.
A "Modified Version" of the Document means any work containing the Document or a portion of it, either copied verbatim, or with modifications and/or translated into another language.
A "Secondary Section" is a named appendix or a front-matter section of the Document that deals exclusively with the relationship of the publishers or authors of the Document to the Document's overall subject (or to related matters) and contains nothing that could fall directly within that overall subject. (Thus, if the Document is in part a textbook of mathematics, a Secondary Section may not explain any mathematics.) The relationship could be a matter of historical connection with the subject or with related matters, or of legal, commercial, philosophical, ethical or political position regarding them.
The "Invariant Sections" are certain Secondary Sections whose titles are designated, as being those of Invariant Sections, in the notice that says that the Document is released under this License. If a section does not fit the above definition of Secondary then it is not allowed to be designated as Invariant. The Document may contain zero Invariant Sections. If the Document does not identify any Invariant Sections then there are none.
The "Cover Texts" are certain short passages of text that are listed, as Front-Cover Texts or Back-Cover Texts, in the notice that says that the Document is released under this License. A Front-Cover Text may be at most 5 words, and a Back-Cover Text may be at most 25 words.
A "Transparent" copy of the Document means a machine-readable copy, represented in a format whose specification is available to the general public, that is suitable for revising the document straightforwardly with generic text editors or (for images composed of pixels) generic paint programs or (for drawings) some widely available drawing editor, and that is suitable for input to text formatters or for automatic translation to a variety of formats suitable for input to text formatters. A copy made in an otherwise Transparent file format whose markup, or absence of markup, has been arranged to thwart or discourage subsequent modification by readers is not Transparent. An image format is not Transparent if used for any substantial amount of text. A copy that is not "Transparent" is called "Opaque".
Examples of suitable formats for Transparent copies include plain ASCII without markup, Texinfo input format, LaTeX input format, SGML or XML using a publicly available DTD, and standard-conforming simple HTML, PostScript or PDF designed for human modification. Examples of transparent image formats include PNG, XCF and JPG. Opaque formats include proprietary formats that can be read and edited only by proprietary word processors, SGML or XML for which the DTD and/or processing tools are not generally available, and the machine-generated HTML, PostScript or PDF produced by some word processors for output purposes only.
The "Title Page" means, for a printed book, the title page itself, plus such following pages as are needed to hold, legibly, the material this License requires to appear in the title page. For works in formats which do not have any title page as such, "Title Page" means the text near the most prominent appearance of the work's title, preceding the beginning of the body of the text.
A section "Entitled XYZ" means a named subunit of the Document whose title either is precisely XYZ or contains XYZ in parentheses following text that translates XYZ in another language. (Here XYZ stands for a specific section name mentioned below, such as "Acknowledgements", "Dedications", "Endorsements", or "History".) To "Preserve the Title" of such a section when you modify the Document means that it remains a section "Entitled XYZ" according to this definition.
The Document may include Warranty Disclaimers next to the notice which states that this License applies to the Document. These Warranty Disclaimers are considered to be included by reference in this License, but only as regards disclaiming warranties: any other implication that these Warranty Disclaimers may have is void and has no effect on the meaning of this License.

2.VERBATIM COPYING

You may copy and distribute the Document in any medium, either commercially or noncommercially, provided that this License, the copyright notices, and the license notice saying this License applies to the Document are reproduced in all copies, and that you add no other conditions whatsoever to those of this License. You may not use technical measures to obstruct or control the reading or further copying of the copies you make or distribute. However, you may accept compensation in exchange for copies. If you distribute a large enough number of copies you must also follow the conditions in section 3.
You may also lend copies, under the same conditions stated above, and you may publicly display copies.

3.COPYING IN QUANTITY

If you publish printed copies (or copies in media that commonly have printed covers) of the Document, numbering more than 100, and the Document's license notice requires Cover Texts, you must enclose the copies in covers that carry, clearly and legibly, all these Cover Texts: Front-Cover Texts on the front cover, and Back-Cover Texts on the back cover. Both covers must also clearly and legibly identify you as the publisher of these copies. The front cover must present the full title with all words of the title equally prominent and visible. You may add other material on the covers in addition. Copying with changes limited to the covers, as long as they preserve the title of the Document and satisfy these conditions, can be treated as verbatim copying in other respects.
If the required texts for either cover are too voluminous to fit legibly, you should put the first ones listed (as many as fit reasonably) on the actual cover, and continue the rest onto adjacent pages.
If you publish or distribute Opaque copies of the Document numbering more than 100, you must either include a machine-readable Transparent copy along with each Opaque copy, or state in or with each Opaque copy a computer-network location from which the general network-using public has access to download using public-standard network protocols a complete Transparent copy of the Document, free of added material. If you use the latter option, you must take reasonably prudent steps, when you begin distribution of Opaque copies in quantity, to ensure that this Transparent copy will remain thus accessible at the stated location until at least one year after the last time you distribute an Opaque copy (directly or through your agents or retailers) of that edition to the public.
It is requested, but not required, that you contact the authors of the Document well before redistributing any large number of copies, to give them a chance to provide you with an updated version of the Document.

4.MODIFICATIONS

You may copy and distribute a Modified Version of the Document under the conditions of sections 2 and 3 above, provided that you release the Modified Version under precisely this License, with the Modified Version filling the role of the Document, thus licensing distribution and modification of the Modified Version to whoever possesses a copy of it. In addition, you must do these things in the Modified Version:

1. Use in the Title Page (and on the covers, if any) a title distinct from that of the Document, and from those of previous versions (which should, if there were any, be listed in the History section of the Document). You may use the same title as a previous version if the original publisher of that version gives permission.
2. List on the Title Page, as authors, one or more persons or entities responsible for authorship of the modifications in the Modified Version, together with at least five of the principal authors of the Document (all of its principal authors, if it has fewer than five), unless they release you from this requirement.
3. State on the Title page the name of the publisher of the Modified Version, as the publisher.
4. Preserve all the copyright notices of the Document.
5. Add an appropriate copyright notice for your modifications adjacent to the other copyright notices.

6. Include, immediately after the copyright notices, a license notice giving the public permission to use the Modified Version under the terms of this License, in the form shown in the Addendum below.
7. Preserve in that license notice the full lists of Invariant Sections and required Cover Texts given in the Document's license notice.
8. Include an unaltered copy of this License.
9. Preserve the section Entitled "History", Preserve its Title, and add to it an item stating at least the title, year, new authors, and publisher of the Modified Version as given on the Title Page. If there is no section Entitled "History" in the Document, create one stating the title, year, authors, and publisher of the Document as given on its Title Page, then add an item describing the Modified Version as stated in the previous sentence.
10. Preserve the network location, if any, given in the Document for public access to a Transparent copy of the Document, and likewise the network locations given in the Document for previous versions it was based on. These may be placed in the "History" section. You may omit a network location for a work that was published at least four years before the Document itself, or if the original publisher of the version it refers to gives permission.
11. For any section Entitled "Acknowledgements" or "Dedications", Preserve the Title of the section, and preserve in the section all the substance and tone of each of the contributor acknowledgements and/or dedications given therein.
12. Preserve all the Invariant Sections of the Document, unaltered in their text and in their titles. Section numbers or the equivalent are not considered part of the section titles.
13. Delete any section Entitled "Endorsements". Such a section may not be included in the Modified Version.
14. Do not retitle any existing section to be Entitled "Endorsements" or to conflict in title with any Invariant Section.
15. Preserve any Warranty Disclaimers.

If the Modified Version includes new front-matter sections or appendices that qualify as Secondary Sections and contain no material copied from the Document, you may at your option designate some or all of these sections as invariant. To do this, add their titles to the list of Invariant Sections in the Modified Version's license notice. These titles must be distinct from any other section titles.

You may add a section Entitled "Endorsements", provided it contains nothing but endorsements of your Modified Version by various parties--for example, statements of peer review or that the text has been approved by an organization as the authoritative definition of a standard.

You may add a passage of up to five words as a Front-Cover Text, and a passage of up to 25 words as a Back-Cover Text, to the end of the list of Cover Texts in the Modified Version. Only one passage of Front-Cover Text and one of Back-Cover Text may be added by (or through arrangements made by) any one entity. If the Document already includes a cover text for the same cover, previously added by you or by arrangement made by the same entity you are acting on behalf of, you may not add another; but you may replace the old one, on explicit permission from the previous publisher that added the old one.

The author(s) and publisher(s) of the Document do not by this License give permission to use their names for publicity for or to assert or imply endorsement of any Modified Version.

5.COMBINING DOCUMENTS

You may combine the Document with other documents released under this License, under the terms defined in section 4 above for modified versions, provided that you include in the combination all of the Invariant Sections of all of the original documents, unmodified, and list them all as Invariant Sections of your combined work in its license notice, and that you preserve all their Warranty Disclaimers.

The combined work need only contain one copy of this License, and multiple identical Invariant Sections may be replaced with a single copy. If there are multiple Invariant Sections with the same name but different contents, make the title of each such section unique by adding at the end of it, in parentheses, the name of the original author or publisher of that section if known, or else a unique number. Make the same adjustment to the section titles in the list of Invariant Sections in the license notice of the combined work.

In the combination, you must combine any sections Entitled "History" in the various original documents, forming one section Entitled "History"; likewise combine any sections Entitled "Acknowledgements", and any sections Entitled "Dedications". You must delete all sections Entitled "Endorsements."

6.COLLECTIONS OF DOCUMENTS

You may make a collection consisting of the Document and other documents released under this License, and replace the individual copies of this License in the various documents with a single copy that is included in the collection, provided that you follow the rules of this License for verbatim copying of each of the documents in all other respects.

You may extract a single document from such a collection, and distribute it individually under this License, provided you insert a copy of this License into the extracted document, and follow this License in all other respects regarding verbatim copying of that document.

7.AGGREGATION WITH INDEPENDENT WORKS

A compilation of the Document or its derivatives with other separate and independent documents or works, in or on a volume of a storage or distribution medium, is called an "aggregate" if the copyright resulting from the compilation is not used to limit the legal rights of the compilation's users beyond what the individual works permit. When the Document is included in an aggregate, this License does not apply to the other works in the aggregate which are not themselves derivative works of the Document.

If the Cover Text requirement of section 3 is applicable to these copies of the Document, then if the Document is less than one half of the entire aggregate, the Document's Cover Texts may be placed on covers that bracket the Document within the aggregate, or the electronic equivalent of covers if the Document is in electronic form. Otherwise they must appear on printed covers that bracket the whole aggregate.

8.TRANSLATION

Translation is considered a kind of modification, so you may distribute translations of the Document under the terms of section 4. Replacing Invariant Sections with translations requires special permission from their copyright holders, but you may include translations of some or all Invariant Sections in addition to the original versions of these Invariant Sections. You may include a translation of this License, and all the license notices in the Document, and any Warranty Disclaimers, provided that you also include the original English version of this License and the original versions of those notices and disclaimers. In case of a disagreement between the translation and the original version of this License or a notice or disclaimer, the original version will prevail.

If a section in the Document is Entitled "Acknowledgements", "Dedications", or "History", the requirement (section 4) to Preserve its Title (section 1) will typically require changing the actual title.

9.TERMINATION

You may not copy, modify, sublicense, or distribute the Document except as expressly provided for under this License. Any other attempt to copy, modify, sublicense or distribute the Document is void, and will automatically terminate your rights under this License. However, parties who have received copies, or rights, from you under this License will not have their licenses terminated so long as such parties remain in full compliance.

10.FUTURE REVISIONS OF THIS LICENSE

The Free Software Foundation may publish new, revised versions of the GNU Free Documentation License from time to time. Such new versions will be similar in spirit to the present version, but may differ in detail to address new problems or concerns. See http://www.gnu.org/copyleft/.

Each version of the License is given a distinguishing version number. If the Document specifies that a particular numbered version of this License "or any later version" applies to it, you have the option of following the terms and conditions either of that specified version or of any later version that has been published (not as a draft) by the Free Software Foundation. If the Document does not specify a version number of this License, you may choose any version ever published (not as a draft) by the Free Software Foundation.

How to use this License for your documents

To use this License in a document you have written, include a copy of the License in the document and put the following copyright and license notices just after the title page:

> Copyright (c) YEAR YOUR NAME.
>
> Permission is granted to copy, distribute and/or modify this document
>
> under the terms of the GNU Free Documentation License, Version 1.2
>
> or any later version published by the Free Software Foundation;
>
> with no Invariant Sections, no Front-Cover Texts, and no Back-Cover Texts.
>
> A copy of the license is included in the section entitled "GNU
>
> Free Documentation License".

If you have Invariant Sections, Front-Cover Texts and Back-Cover Texts, replace the "with...Texts." line with this:

> with the Invariant Sections being LIST THEIR TITLES, with the
>
> Front-Cover Texts being LIST, and with the Back-Cover Texts being LIST.

If you have Invariant Sections without Cover Texts, or some other combination of the three, merge those two alternatives to suit the situation.

If your document contains nontrivial examples of program code, we recommend releasing these examples in parallel under your choice of free software license, such as the GNU General Public License, to permit their use in free software.